Health-related quality of life in patients with end-stage renal disease receiving chronic dialysis treatment

A population based study

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Table of contents

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List of papers

The following thesis is based on three publications, all referred to by Roman numerals:

Paper I

Østhus TBH, Dammen T, Sandvik L, Bruun CM, Nordhus IH, and Os I. **Health-related quality of life and depression in dialysis patients: Associations with current smoking.** Scand J Urol Nephrol. 2010 Feb; 44(1): 46-55.

Paper II

Østhus TBH, Preljevic VT, Sandvik L, DammenT and Os I. **Renal transplant acceptance status, health-related quality of life and depression in dialysis patients.** J Ren Care. 2012 Jun;38(2):98-106.

Paper III

Østhus TBH, Preljevic VT, Leivestad T, Sandvik L, Nordhus IH, Dammen T and Os I. **Mortality and Health-related quality of life in prevalent dialysis patients: Comparison between 12-items and 36-items Short-Form Health Survey.** Health Qual Life Outcomes. 2012 May 6; 10(1):46.

List of appendices

Abbreviations

BMI	Body Mass Index (kg/m^2)
BDI	Beck Depression Inventory
CCI	Charlsons modified comorbidity index
CDI	Cognitive Depression Inventory
CI	Confidence interval
CKD	Chronic kidney disease
DD	Deceased donor
ESRD	End-stage renal disease
HD	Hemodialysis
HR	Hazard ratio
HRQOL	Health-related quality of life
KDQOL SF	Kidney disease quality of life short form
LD	Living donor
MCS	Mental component summary score
NRR	Norwegian Renal Registry
NS	Non significant
OR	Odds ratio
PCS	Physical component summary score
PD	Peritoneal dialysis
RTX	Renal transplantation
RRT	Renal replacement therapy
SF-12	Short form-12 health survey
SF-36	Short form-36 health survey
SPSS	Statistical package for social sciences

Introduction

This thesis addresses health-related quality of life (HRQOL) in a heavily burdened patient population, namely patients with end-stage renal disease (ESRD) in chronic dialysis treatment. For an understanding of the multi-factorial concept of HRQOL in patients with chronic illness, a wide spectrum of research approaches is required. Today, validated self-administered questionnaires are the method of choice for assessing HRQOL. Simultaneously, a broad collection of demographic and clinical characteristics that possibly have impact on patients HRQOL should be registered in a clinical trial. By achieving a more comprehensive understanding of how ESRD affects HRQOL, and how HRQOL affects clinical status and outcome in ESRD patients, health care offered to these patients may be improved.

Definition and epidemiology of end-stage renal disease (ESRD)

ESRD represents a clinical condition in which there has been an irreversible loss of renal function of a degree sufficient to render the patient permanently dependent of renal replacement therapy (RRT, dialysis or transplantation) for survival. This general accepted definition is an operational one, and not defined by a certain level of glomerular filtration rate or other objective threshold (1). ESRD is included in the term chronic kidney disease (CKD) stage 5, i.e. glomerular filtration rate (GFR) $\leq$ 15 ml/min. The most common causes of ESRD are hypertension, diabetes, glomerulonephritis, interstitial nephritis and polycystic kidney disease.

Incidence and prevalence of patients in need of RRT are increasing worldwide. Increasing prevalence of hypertension and diabetes, as well as increased life expectancy in aging populations, contribute to the increase (2;3). As a consequence of improved treatment and survival of patients with cardiovascular disease during the last decades, more patients with CKD will more likely progress to ESRD.

Mortality rates for ESRD patients in dialysis remain unacceptably high, despite technological advances in dialysis treatment and improvements in the management of cardiovascular risk factors. Some improvements have been reported, as seen in recent data from UK in which 1-year survival

during the last decade has improved from 65% to 75% in patients ≥65 years (4). For ESRD patients in Europe and in the United States, 1-year survival rates after initiation of dialysis treatment are 81.1 % and 80.4 % respectively (5;6). The corresponding survival rates after five years are 38.2 % and 35.8 % (5;6).

Renal replacement therapy

Chronic renal replacement therapy (RRT) includes either dialysis (hemodialysis or peritoneal dialysis) or renal transplantation.

Hemodialysis (HD)

The majority of patients worldwide on RRT receive HD, more than 1 million patients. The patient's blood is delivered to the dialyzer ("artificial kidney") through an extracorporeal circuit. The transfer of water, waste products, and other solutes occurs through the semi-permeable membrane separating the blood from the dialysate. HD usually takes place in specialized dialysis units, but is also undertaken in satellite units and at home. HD is usually done for four hours three times weekly. Increased frequency of dialysis improves efficiency and outcome (7), and this may also urge increased use of home hemodialysis. Patient's personal preference should be taken into consideration when treatment modality for RRT is chosen.

Peritoneal dialysis (PD)

PD is used in variable frequencies in different countries, but there has been an increase in the use of this dialysis modality, currently approximately 150 000 patients worldwide. This is mainly a home-based therapy, and the success is based on the patient's or a caregiver's ability or competence to undertake PD. This necessitates a teaching period in the hospital setting, usually in an outpatient clinic. Both continuous ambulatory peritoneal dialysis with manual shift of the dialysate or use of automatic devices taking care of the shifts of the dialysate in and out of the abdominal cavity, and usually during night-time, are used. The peritoneal cavity is filled with fluid (dialysate), and the peritoneal membrane serves as endogenous dialyzer. Across the peritoneal membrane, waste products, electrolytes and water

diffuse from the capillaries to the dialysate, a hyper-osmotic fluid, usually containing glucose.

The HD and PD treatment modalities are equal in some aspects, but patients are often chosen for PD based on the ability to cope with the treatment, cardiovascular instability, and to preserve residual renal function. The selection criteria can vary between dialysis centres according to clinical traditions.

Renal transplantation (RTX)

RTX is considered the optimal treatment for patients with ESRD due to enhanced survival (8), improved HRQOL (9) and lower costs (10). Unfortunately, not all patients will receive a renal transplant due to lack of donor organs or comorbidity that offset the benefit of RTX. Recipients undergo a thorough medical workup and evaluation before they are accepted for RTX. The renal graft is provided either from a deceased donor or from a living donor. Living with a functional renal graft frees the patient from the exhausting dialysis treatment, yet lifelong immunosuppressive medication is mandatory to avoid graft rejection. Usually patients spend a variable duration of time (up to years) awaiting RTX, but pre-emptive RTX (before dialysis is needed) are also used in a small proportion of the patients. The possibility to get a renal transplant varies greatly between countries, even between the Nordic countries.

The Norwegian dialysis population

Currently the number of patients on dialysis treatment is escalating, as an increasing number of patients enter into RRT program without possibilities for future transplantation. Figure 1 demonstrates the status of RRT in Norway from 1982 to the end of 2009. As the incidence of patients accepted for RRT has increased during the last years in Norway (reaching 116.3 per million inhabitants by the end of 2009), the number of patients receiving chronic dialysis has increased even more. Number of patients in Norway that will be in need of RRT has been estimated to increase 10 % per year from 2005 to 2015 according to an expert group in the Norwegian Health Directorate (http://www.nephro.no/foreningsnytt/rapportdialyse2006.pdf), which would result in more than a doubling of the Norwegian dialysis population in 10 years.

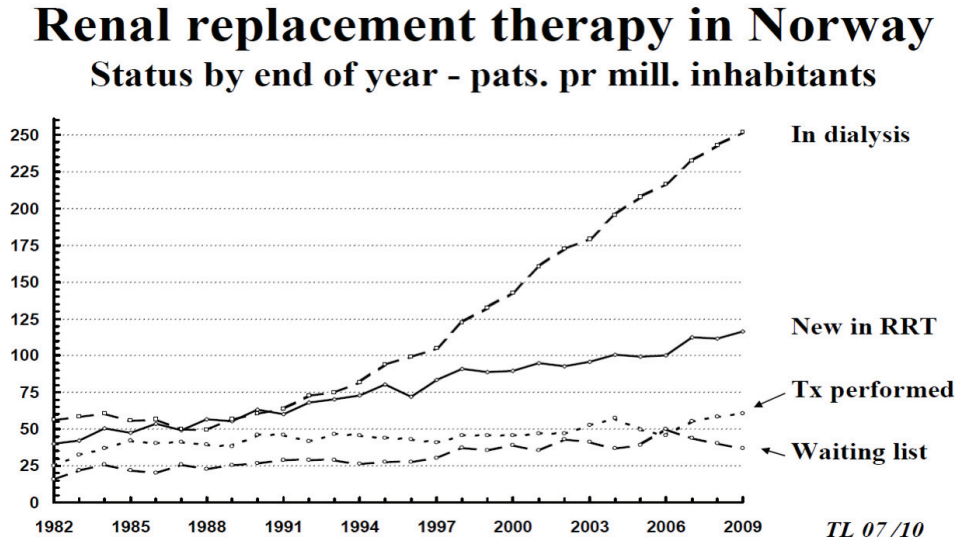


Figure 1. From Annual Report 2009, the Norwegian Renal Registry(11). Courtesy of Torbjørn Leivestad

Dialysis modalities

Data from the Norwegian Renal Registry 2009 expose that approximately 80% of the prevalent dialysis patients in Norway receive HD. The use of PD varies widely even between renal units in Norway, from 10-30%, and surprisingly more frequently used in some urban areas than in rural areas. This is mainly due to tradition and experience with PD. More frequent use of home -based therapy is encouraged. Small satellite units for HD are established in rural areas in Norway to avoid long travel distances. Home hemodialysis is still rarely used in Norway.

Eligibility for renal transplantation

In Norway, all patients approaching or entering dialysis, are considered for renal transplantation. Eligibility for transplantation is based on medical and surgical criteria, and not limited by social or economic status. Age and gender have not been discriminating factors (12-14). In 2009, 66% of the incident dialysis patients were considered potential candidates for transplantation, while 34 % were accepted for lifelong dialysis. The most common contraindication for renal transplantation has been severe

cardiovascular and peripheral artery disease. Severe mental illness and dementia may limit access to the waiting list, while malignant diseases considered cured pose no absolute contraindication and most patients can enter the transplantation programme if they are cancer free after a limited period.

The availability of kidneys is limited, making patients spend months to years in dialysis. Not only is the monetary cost tremendous, approximately 500000-1000000 NOK yearly per patients in hemodialysis (little data available on the total cost), including costs of health personnel, travel to dialysis 3 or 4 times a week, dialysis treatment and medications. But also the individual human burden of entering dialysis treatment is huge. The majority of patients lose their workability in the course of the disease, i.e. when entering dialysis.

Renal transplantation in Norway

The renal transplantation rate is high in Norway, reaching 60.5 per million inhabitants in 2009, where 36% of the transplanted kidneys came from a living donor (11). Thus, the majority of patients on RRT in Norway are transplanted, and they constitute more than 2/3 of the RRT population. In 2009, the median time on the waiting list for RTX was 8 months (range up to 74 months) for patients receiving renal graft from a deceased donor. Currently the RTX activity is increasing. Because of the high transplantation activity, the Norwegian dialysis population is characterized by a rather short time in dialysis compared to other countries.

Definition of health-related quality of life (HRQOL)

HRQOL is a multidimensional concept that includes a person's perception of physical functioning, social role functioning, mental health, and general health (15). Three of these domains appear in the World Health organization's definition of health as a "state of complete physical, mental and social well-being and not merely the absence of infirmity and diseases" (16). Because the clinicians are interested in how a particular disease and the treatment of the disease affect a patients experience of health, the term "health-related quality of life" may be more adequate than simply "quality of life". Multiple aspects of life exist that are not generally considered as "health," including income, freedom, and quality of the environment. Nevertheless, these aspects may influence on a person's

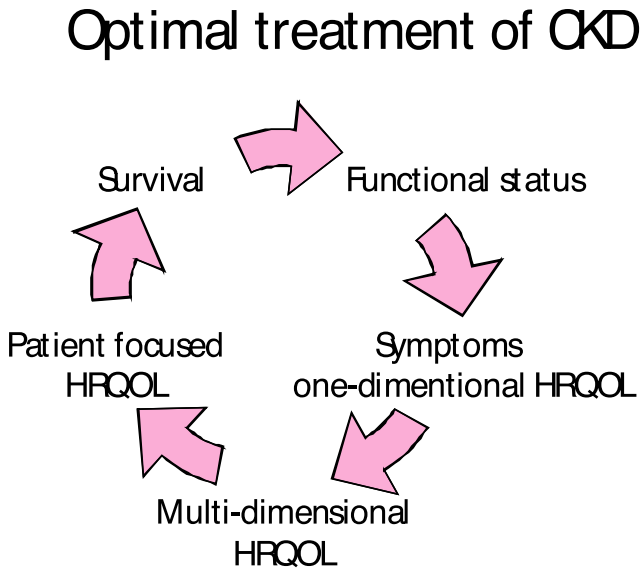
experience of health. When a patient is ill or diseased, almost all aspects of life can become health related (17). It is important to note that the subjective experience of health is influenced by a person's beliefs, expectations and perceptions(15).

HRQOL measurements are based on a patient's own (''subjective'') sense of well-being, and the quantitatively HRQOL scores are calculated from self-reported questionnaires. In patients with chronic illness, HRQOL assessments may be used in patient care to screen for and prioritize problems, to improve communication between health care workers and patients, and to evaluate response to treatment(18). Frequently used HRQOL instruments have been validated in numerous studies and long version questionnaires have been transformed into short versions (19-21). Simpler questionnaires containing even fewer items are warranted. Tailor-made instruments containing domains that can be weighted differently by different patients, according to which domain they consider most important in their lives, has been called for(18). In this thesis the term HRQOL is used, irrespectively of whether generic or disease specific HRQOL measures are described.

HRQOL in ERSD patients

Figure 2 (modified after Kalantar-Zadeh & Unruh) demonstrates the evolution of views on the optimal treatment of CKD (18). From focusing on RRT as a life-saving treatment, and survival the outcome of interest, functional status and self-perceived HRQOL has gained increased attention from clinicians during the last three decades. The first studies addressing functional status in ESRD patients used instruments like the Karnofsky performance scale (22;23). When using the Karnofsky performance scale, the patients' level of functioning is evaluated and rated by others (health care personal). According to the present standard, by collecting self-reported HRQOL from validated questionnaires, it is the patients themselves that have the "rating role". As numerous studies have reported strong associations between self-reported HRQOL and survival (24-30), we may assume that improving HRQOL can improve health and survival further. Further research is needed to elaborate this.

There has been a marked increase in number of publications concerned with HRQOL in dialysis patients. Figure 3 demonstrates number of publications registered in www.pubmed.com by using the two search connotations "health-related quality of life" and "dialysis" (the search was



Modified after Kalantar-Zadeh & Unruh. Int J Urol Nephrol 2005.

Figure 2. The evolution of views on the optimal treatment of CKD.

performed on the 15th of September 2011). No publications were found up to 1970, and 40 in the time period 1st January 1970 to 31st of December 1979. During the last decade (from 1st of January 2000, until 31st of December 2009), a total number of 1972 publications appeared in the Pub Med search, demonstrating an exponential rise of attention towards this topic. During this period, 2 articles were found that included Norwegian renal patients (31;32).

Several studies have reported that HRQOL is substantially impaired in dialysis patients compared to general populations (33-38). Data from the large Dialysis Outcomes and Practice Patterns Study (DOPPS) have demonstrated that HD patients from the United States, Europe, and Japan had much lower PCS and MCS scores than the normative values for their respective populations (39). Also when compared to patient populations with other chronic illnesses, like diabetes, chronic pulmonary diseases, rheumatic diseases and cardiovascular diseases, HRQOL seems especially compromised in ESRD patients (40). While HRQOL has been assessed in other patient populations like patients with rheumatic disease(41), there has been a paucity of data from Norwegian dialysis patients. Physical factors

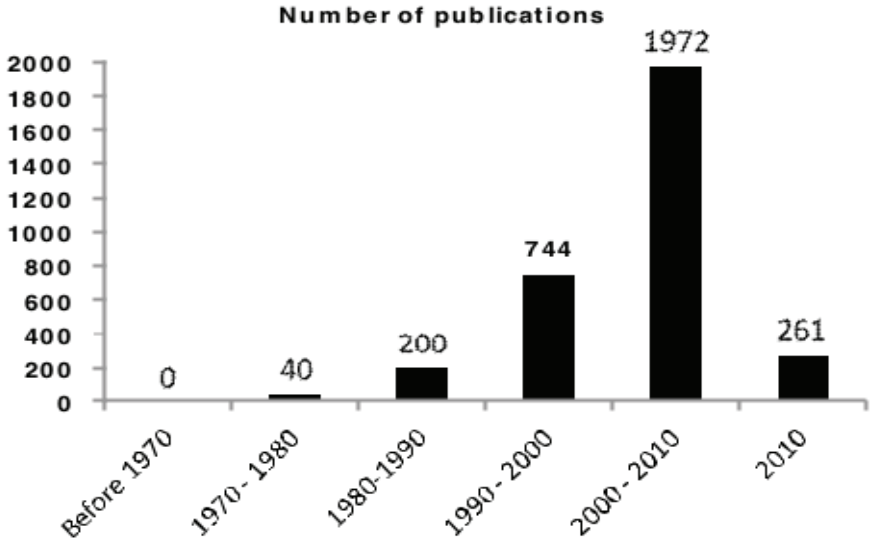


Figure 3. From a Pub Med search on the terms "health-related quality of life" and "dialysis", number of publications (abscissa) by time (ordinate) are shown. The search took place in September 2011. Decades (i.e. 1st of January 1970 until 31st of December 1979) are shown; in addition number of publications from the year 2010 is shown in the column to the utter right.

such as levels of hemoglobin, albumin, psychosocial factors such as marital status, depression, and anxiety levels; together with sociodemographic and clinical factors such as age, gender, duration of renal disease and dialysis, comorbidity (e.g. diabetes), all seem to have significant effects on HRQOL in HD and PD patients (42;43). Further research assessing cross-cultural differences in impact of chronic medical conditions on HRQOL have been called for to explain reported variations (44). In ESRD patients receiving HD, differences in HRQOL scores have been reported between countries. Japanese HD-patients reported better physical functioning than HD-patients in the United States or Europe, but they also reported the highest burden of kidney disease (39). Due to cultural differences, it is of high importance to assess HRQOL in a representative population of Norwegian dialysis patients.

Research regarding HRQOL in HD and PD patients has yielded somewhat conflicting results. A meta-analysis performed by Cameron et al (45) showed that ambulatory PD patients perceived greater well-being than in-centre HD patients; the latter were associated with greater distress (45). Because patients are not randomly assigned to HD and PD treatments,

treatment groups frequently differ with respect to many characteristics that may be associated with HRQOL, such as age and comorbid illnesses. Data from the Northern Thames study (46) indicates that PD in elderly dialysis patients is associated with better disease specific HRQOL than HD. Due to lack of previous Norwegian data it was important to assess HRQOL in a representative sample of both HD and PD patients.

Renal transplantation is expected to improve HRQOL in dialysis patients (47;48). However, there is a paucity of data reporting whether acceptance status for renal transplantation affects HRQOL in dialysis patients. Figure 4 demonstrates the process of referral and planning of renal transplantation in CKD patients (49). Initiation of pre-transplant investigations may start at different moments during the course of CKD. Thus, patient with CKD may be accepted for RTX before the onset of dialysis (with possibility for pre-emptively transplantation), or after dialysis initiation (Figure 4). This means, that when assessing HRQOL in prevalent dialysis patients, patients will differ in regard to their prospect of being transplanted or not. Dialysis patients have been suggested to cope better with dialysis if treatment is temporary and preceding RTX, rather than permanent and deprived of any prospect of RTX (50). Comparative studies, though small, have shown lower depression scores in kidney transplant patients compared to dialysis patients (51-53), a result confirmed in a longitudinal study of 88 dialysis patients who underwent RTX (54). To the best of our knowledge, no studies have explored whether dialysis patients waiting for RTX have better HRQOL and less depression compared to those who have been rejected for RTX. In a recent study Kuntz et al examined prevalence of psychiatric distress by using the Patient Health Questionnaire in a sample of 518 ESRD patients at the specific time point immediately upon initial referral to a transplant center(55). The prevalence of depression was lower than expected (15.1 %), but the authors point to the lack of clarity in the literature about renal patients' self-report of psychological distress during the critical moments of initial consideration for transplant(55). It is important to achieve a better understanding of how acceptance status for RTX affects HRQOL in dialysis patients. Especially because some patients are rejected for this treatment, and an increasing number of patients are recruited into life-long dialysis.

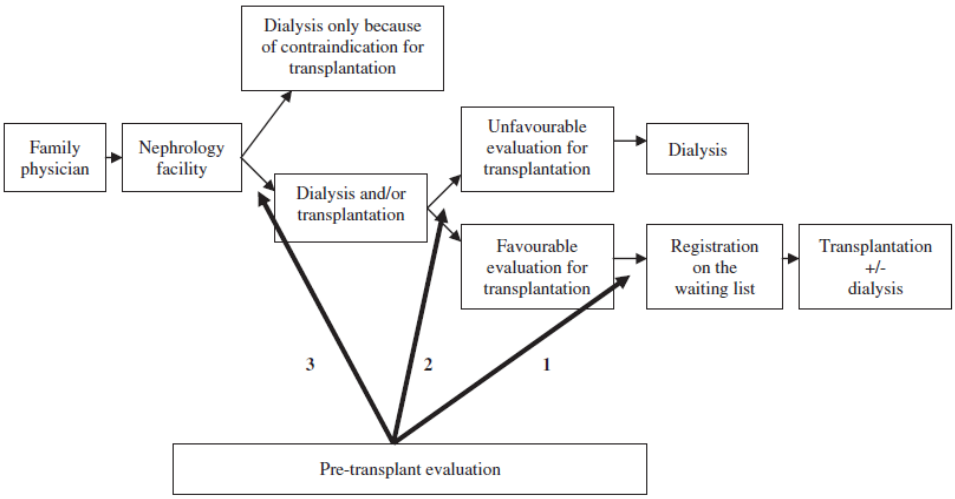


Figure 4. The process of planning for RRT for patients in the NEPHROLOR network. Evaluation of a potential transplant recipient could start at three different moments during the course of chronic kidney disease: very early referral to a nephrologist with acceptance for renal transplantation before starting dialysis and possible pre-emptive transplantation (arrow 1), concurrent evaluation for planned dialysis and acceptance to renal transplantation (arrow 2) and late referral with dialysis start in an emergency setting and pre-transplant evaluation starting after onset of dialysis. Bayat S et al. Nephrol Dial Transplant 2006 ;21: 2900-7. The Figure is adapted with kind permission from the authors (49).

Improved HRQOL has become a well acknowledged treatment goal in patients with ESRD (50). HRQOL is both an important outcome of health care and a major determinant of outcome because a close relationship exists between QOL, morbidity and mortality (24;25). The importance of identifying modifiable factors that affects HRQOL in this burdened patient population cannot be overemphasized. Despite this knowledge, there was a paucity of data regarding HRQOL in the Norwegian dialysis population until recently. Figure 5 gives an overview of the aspects addressed in the cross-sectional part of the present study, which will be discussed in the thesis (paper I-III). Furthermore, the impact of HRQOL on mortality (paper III), and the effect HRQOL or depression on the likelihood of receiving a renal transplant (paper II) are reported based on longitudinal data.

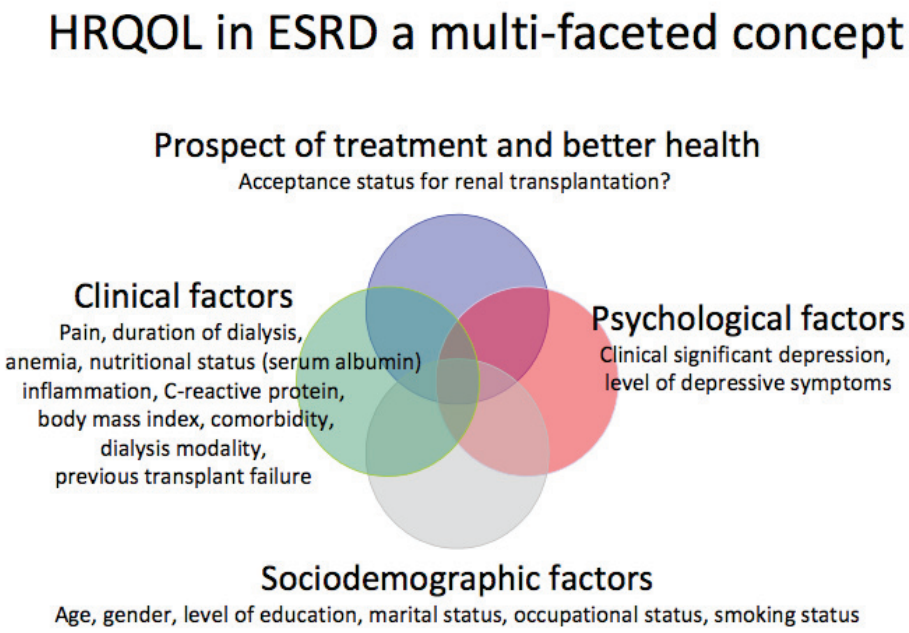


Figure 5. Different aspects that may have impact on HRQOL in ESRD patients: markers of present clinical condition, acceptance status for renal transplantation, presence of clinical significant depression and level of depressive symptoms, as well as sociodemographic factors are all assessed in the thesis (paper I–III).

Tools to measure HRQOL in ESRD patients

To assess HRQOL, validated self-administered questionnaires are applied. A combined approach, using generic measurement augmented by disease-specific measurement is the recommended strategy (17;19). The Medical Outcome Study 36-item Short Form Health Survey (SF-36)(56) is a patient self-reported measure of HRQOL that has been used and validated among the general population and among various disease populations, including patients with kidney disease. The SF-36 captures the multidimensional nature of HRQOL, measuring 8 domains of functioning and also yielding component summary scores for the 2 primary dimensions of functioning: physical (PCS) and mental (MCS). The SF-12 (57), a shortened version of the SF-36 questionnaire was originally designed to reproduce component summary scores based on fewer items than the SF-36. The SF-12 contains a subset of 12 items from the SF-36, including one or two items from each of the eight SF-36 subscales (57). In the U.S. general population, the SF-12

summary scores (PCS-12 and MCS-12) based on the 12 items, explained more than 90% of the variance in the SF-36 physical (PCS-36) and mental (MCS-36) component summary scores (57). Yet, the SF-12 has been rarely used for patients on dialysis, despite the advantage that it comprises only one third of the items compared to SF-36 (58). Specific kidney disease related quality of life was assessed in the present study by using the KDQOL-SF version 1.3 (59).

Depression in ESRD

Depression is reported to be the most common psychological problem presented by patients maintained on dialysis therapy (60;61). Depression is associated with poorer clinical outcomes and depression is potentially treatable in dialysis patients. Thus, it is important for dialysis units to develop strategies for screening, assessing and treating dialysis patients for clinical significant symptoms of depression (62). Relatively recent epidemiological evidence suggest that the rate of psychiatric disorders in the ESRD population is substantially higher than that observed in other chronic medical conditions (63). Estimates of the prevalence of depression in ESRD patients are particularly high, suggesting that 12-40% meet diagnostic criteria for a mood disorder(64).

Researchers in the field of renal disease have often not distinguished between the diagnosis of major depression and high levels of depressive affects. Assessment of depressive affects has often been conducted with Beck Depression Inventory (BDI)(65). This inventory assesses both somatic and psychological aspects of depression. Neurovegetative symptoms of depression, including fatigue, cognitive deficits, decreased appetite, insomnia, and loss of libido, may occur secondary to chronic renal failure and in the absence of a depressive syndrome. Additionally, conditions associated with ESRD such as anemia, diabetes, and electrolyte disturbances, may mimic depressive symptoms (66). The assessment and diagnosis of depression in ESRD patients, is complex because of the potential symptom overlap between the two conditions. Neither the level of depressive symptoms nor the prevalence of clinical significant symptoms of depression had previously been assessed in Norwegian dialysis patients. It was therefore of high importance to explore this in a representative sample of Norwegian dialysis patients.

Smoking and depression

Epidemiological data have demonstrated a strong association between smoking and depression (67-70). Little is known about this association in dialysis patients. Few studies have addressed this relationship in ESRD patients, but in a recent Danish study from 2007, smoking was found to be associated with worse scores on a number of HRQOL scales in 130 dialysis patients (71). Smoking has also been highlighted as an independent predictor of poor HRQOL in a longitudinal study of adults with diabetes (type 1 diabetes: n=490, and type 2 diabetes: n=1147) published in 2011 (72). Increased focus on lifestyle factors, including smoking, was pointed out in order to improve HRQOL in these patients. Smoking is a well-known risk factor for cardiovascular disease in ESRD patients(73). Yet, little is still known about the relationship of smoking with HRQOL in ESRD patients. As smoking is a potential modifiable factor, it is necessary to gain more knowledge about how smoking associates with HRQOL and depression in ESRD patients.

Hypothesis

Given this background, we hypothesized that

- HRQOL would be compromised in Norwegian dialysis patients compared with the general Norwegian population, and clinical significant symptoms of depression would be prevalent (paper I).

- Smoking would be associated with reduced HRQOL and increased level of depressive symptoms in dialysis patients (paper I).

- Patients who are not accepted (rejected) for RTX and facing life-long dialysis treatment experience reduced HRQOL and higher levels of depressive symptoms than patients accepted for RTX (paper II).

- Component summary scores from SF-12 and SF-36 are highly correlated in dialysis patients (paper III).

- Self-assessed HRQOL based on the SF-12 and the SF-36 component summary scores would provide similar predictions of mortality in patients on dialysis (paper III).

Aims of the study

- To explore both HRQOL and prevalence of clinical significant symptoms of depression in Norwegian chronic dialysis patients (paper I).

- To study possible associations between HRQOL, depression and current smoking status in dialysis patients (paper I).

- To compare HRQOL and depression in dialysis patient accepted or rejected for RTX (paper II).

- To investigate whether HRQOL or depression predict the likelihood of RTX in patients still awaiting a decision on RTX acceptance (paper II).

- To assess HRQOL with SF-12 and SF-36 component summary scores, and compare their abilities to predict mortality in chronic dialysis patients, after adjusting for traditional risk factors (paper III).

Material and methods

Study design

A cross-sectional design was chosen for the explorative part of the study. As the catchment area exceeded 1 million inhabitants, the study is considered population based. Information of HRQOL, depression, clinical and sociodemographic data were collected cross-sectionally. HRQOL impairments and prevalence of depression could be estimated based on the cross-sectional data. The study patients were followed for 3-4 years. Time of death, cause of death and time of renal transplantation were registered in the prospective longitudinal study. Thus, the effect of HRQOL on mortality and on the likelihood of renal transplantation could be assessed.

Patients and recruitment procedure

Prevalent dialysis patients from 10 different hospitals (five university hospitals and five regional hospitals) from different parts of Norway (Health Regions North, West, and South-East) participated in the study. The study centers provide renal health care for more than two million Norwegian inhabitants, close to half of the total Norwegian population. Two of the centers supply health care mainly for an urban population, whereas the other hospitals receive patients from both rural and urban areas. The following centers participated in the present study: Akershus University Hospital, Østfold Regional Hospital, Vestfold Regional Hospital, Buskerud Regional Hospital, Elverum Hospital, Lillehammer Hospital, Stavanger University Hospital, Haukeland University Hospital, Tromsø University Hospital, and Oslo University Hospital Ullevål.

Inclusion criteria:

- Age ≥ 18 years
- Maintenance dialysis (HD or PD) for 2 months or more
- Clinically stable condition during the last 4 weeks
- Adequate oral and written Norwegian language skills
- Signed, informed consent

Exclusion criteria:

- Cognitive dysfunction (dementia or mental retardation)
- Psychosis or drug abuse

• Hospitalization during the investigation period excluded patients from the study; however, they could be enrolled four weeks or more after discharge from hospital if they were clinically stable.

Recruitment procedure

Dialysis patients were enrolled in the study consecutively from August 2005 to February 2007. A total of 530 dialysis patients at the study centers were evaluated for study participation (see flowchart, Figure 6). Of the 416 patients considered eligible for the study, 326 patients consented to study participation, and 301 could be enrolled (enrollment rate of 72.4%, Figure 6). The data from the cross-sectional study could be linked with data on mortality and transplantation in the Norwegian Renal Registry (NRR). In January 2010, data on time of death, cause of death and time of renal transplantation were collected from the NNR, and coupled with the cross-sectional data. The median follow-up time for the prospective part of the study was 3.6 years, and none of the patients were lost from follow-up.

Before starting the data collection, informative lectures about the study were held for the staff at all study centers. Afterwards, especially dedicated study personnel (one or two nurses from each center, usually one working with HD and one working with PD), attended a seminar held at Oslo University Hospital Ullevål to learn about the aims and methodology of the study. This was done in order to enhance standardized use of the instruments.

After the patients consented to study participation, they were included in the study. Clinical and sociodemographic data were collected. Hemodialysis patients answered the self-administered questionnaires during the dialysis treatment. A trained study doctor or study nurse gave instructions in how to answer the questionnaire to the patients at time of study inclusion, and was available for assistance if needed. If assistance was necessary, the patients were dialyzed in a separate room to secure discretion. None of the HD patients in this study received the questionnaire by post. Most patients completed the questionnaire during one dialysis session. PD patients were informed about the questionnaires in a similar way during a regular visit at the outpatient clinic. Most of them were able to answer the questionnaire during their stay in the outpatient clinic at a regular visit. Some of the PD patients brought the questionnaire with them home, if spending time in hospital was not feasible. All questionnaires were returned.

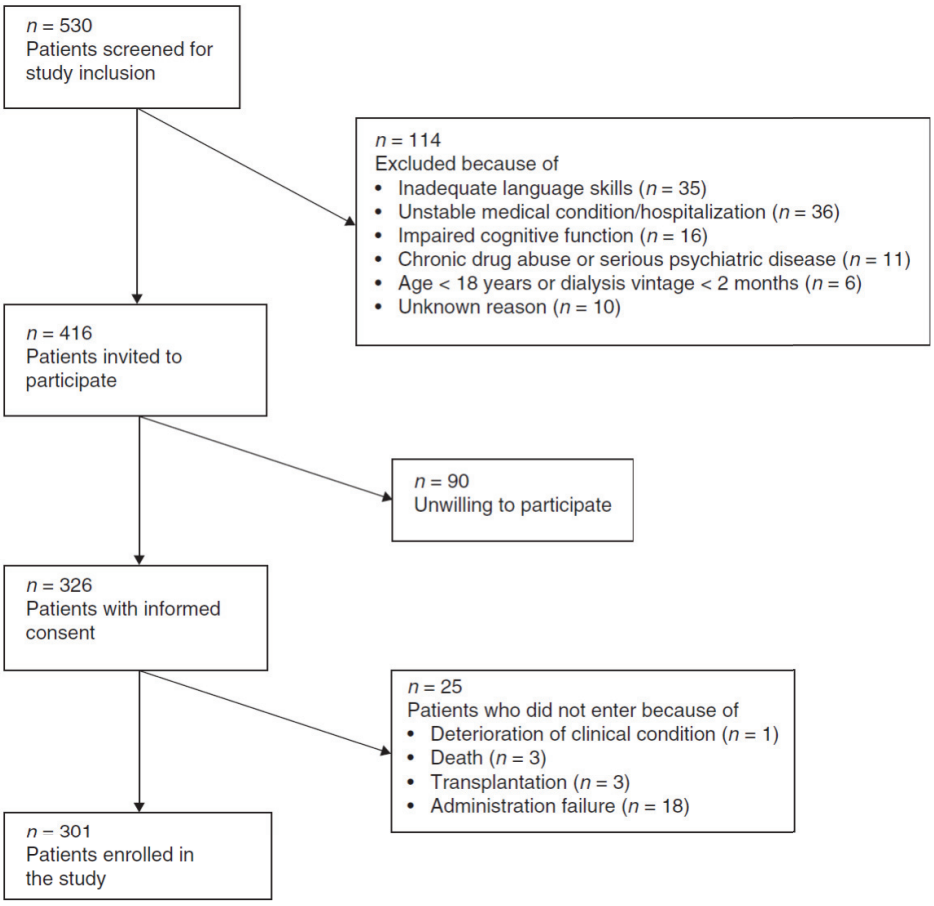


Figure 6. Flowchart of the recruitment process (paper I, (74))

Demographic and clinical data collection

Data collected for the cross-sectional study (Paper I) were used as baseline data in the prospective studies (Paper II and Paper III).

Demographic data

The study doctor or nurse completed the Clinical report form, containing both demographic and clinical data, before the patient answered the questionnaires. Demographic data included age, gender, marital status, education, work status and information on smoking habits. The clinical and

laboratory data were collected from reviews of hospital charts. Demographic data were attained by reviews of hospital charts and questionnaires, in addition to direct questioning the patients.

Data on smoking habits

Information about current smoking status (yes/no) and number of daily smoked cigarettes was collected by direct verbal questioning the patients ("do you smoke?" and "how many cigarettes do you smoke a day?), at the time of study inclusion. Additionally, cross-checking with available information in the hospital's charts was done. The credibility of this information was considered high, due to the frequent communication between patients and health personal, and the time spent in the hospital. Data on previous smoking habits and number of daily smoked cigarettes were gathered in self-administered questionnaire at the time of the study.

Clinical data

Cause of renal failure, dialysis modality, dialysis vintage, comorbidities, history of previous renal transplantation, present acceptance for renal transplantation status, and clinical and laboratory data were collected from the hospital charts. Laboratory data like hemoglobin, albumin, C-reactive protein, total cholesterol were obtained from the monthly routine blood sampling, the last one taken before study participation. Predialysis blood pressure was registered at three separate dialysis session, the session at the study inclusion day and the two preceding adjacent sessions. An average of the three measurements could be estimated. Body mass index was calculated from height and bodyweight (weight was measured predialysis for HD patients, and for PD patients without dialysate fluid in the peritoneal cavity).

Data on acceptance status for renal transplantation

Acceptance status for renal transplantation was categorized as accepted (on waiting list for deceased kidney transplant, or accepted for living donor transplantation), pending status i.e. considered as a potential candidate for transplantation but awaiting a decision, or rejected.

The Charlson Comorbidity Index

Comorbidity was measured using the modified Charlson Comorbidity Index (CCI). The CCI has been validated for dialysis patients and found to be a strong predictor of clinical outcomes (75). The CCI is a composite score of 17 comorbid conditions and age. Comorbid conditions are given scores ranging from 1 to 6, and a score of 1 was added for each decade over 40 years of age. In this study, CCI was also calculated without including age to evaluate the effect of age as a separate factor in multivariate analysis. Figure 7 summarizes the comorbid conditions included in the CCI, and their scores.

Comorbidity score	Conditions (n=17)
1	Coronary artery disease
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disorder
	Peptic ulcer disease
	Mild liver disease
	Diabetes
2	Hemiplegia
	Severe renal disease
	Diabetes with end-organ damage
	Any tumours, leukaemia, lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumour
	AIDS

Figure 7. Charlsons Comorbidity Index

Questionnaires

The Kidney Disease and Quality of Life Short Form, version 1.3, (KDQOL-SF) (59) was applied to assess HRQOL. The Medical Outcome Study 36-item Short Form Health Survey (SF-36) (56) was administered as the first part of the KDQOL-SF, to measure generic dimensions of HRQOL.

SF-36

It consists of 36 items, 35 of which form eight multi-item scales: physical function, role limitation because of physical problems, bodily pain, general health perception, vitality, social functioning, role limitation because of emotional problems and mental health. Two component summary scores are derived from the eight subscales: the physical component summary scale (PCS) and the mental component summary scale (MCS). A Norwegian version of the SF-36 has been validated (76), and population norms established (77).

SF-12

The embedded SF-12(57) comprises 12 questions from the SF-36, and the component summary scores of SF-12 were calculated with the algorithm from the KDQOL working group (http://gim.med.ucla.edu/kdqol/downloads).

KDQOL-SF 1.3

The KDQOL questionnaire was developed by the Rand group in 1990 (59) to address kidney disease-specific HRQOL. Forty-three items are classified into 11 specific kidney-related scales: symptoms, effect of kidney disease, burden of kidney disease, work status, cognitive function, quality of social interactions, sexual function, sleep, social support, dialysis staff encouragement and patient satisfaction. The KDQOL-SF has been applied in several international studies on dialysis patients(42), and in a Scandinavian population (78). The questionnaire was translated into Norwegian and back-translated to American English, as instructed by the Rand group. Rigorous back-translation and pre-testing of the kidney specific scales were done, before consensus in the research group was made (appendix I).

All the SF-36 subscales and the 11 specific kidney-related scales were scored independently and given a score from 0 to 100; a higher score indicates a more positive state. The MCS and PCS scores were standardized to a general population mean of 50 and a standard deviation of 10 (i.e. T-score metric) by using the U.S.-derived scoring algorithm proposed by Ware et al (79). Thus a score above or below 50 indicates a state above or below average functioning.

The Beck Depression Inventory

The Beck Depression Inventory (BDI) self-administered questionnaire was applied to measure the level of depressive symptoms (appendix II). BDI has been used in both the general and CKD populations (80;81). It consists of 21 items that examine the somatic and cognitive effects of depression. Each item is scored from 0 to 3, where a higher score indicates a higher level of depressive symptoms. A BDI score greater than 14 (Paper I), and a BDI score greater that 15 (paper II) was used as the cut-off values for clinical significant depression in the current study, based on previous reports (65;82). A Cognitive Depression Index (CDI) consisting of 15 BDI items was generated to evaluate depressive symptoms without including the somatic aspects of depression (83).

Ethical considerations

The National Committee for Medical and Health Research Ethics in Norway approved the study protocol in June 2005. Concession was obtained from the National Data Inspectorate. Written informed consent after oral and written information about the study was a prerequisite for study participation.

The database

An electronic database was constructed on a specific domain ("Vilje") of the research data server in Oslo University Hospital Ullevål (OUS-U). All data are stored in deidentified form, without patients' name, date of birth or identification number. Raw data in paper-form were stored in a double locked room, and the cross-code key stored in a different location, according to the directions given in the permission from the Data Inspectorate. Deidentified data can be stored until 2025. Data on only four non-sensitive variables could be registered for the eligible patients who did not participate in the study: age, gender, modality of dialysis and dialysis vintage.

Statistical methods

Overall statistical methods

In descriptive analyses, clinical, demographic, and HRQOL variables were expressed as means and standard deviations (SDs) for symmetrically distributed variables, or medians with interquartile ranges (IQR), when data were skewed. Normal distributions were assessed by visual inspections of histograms. Percentages were used for categorical variables. One-way analysis of variance (ANOVA) with post-hoc Bonferroni adjustment, or Kruskall-Wallis tests for skewed data were used to compare continuous variables among more than two groups, and Student's t-test or the Mann-Whitney test for skewed data was applied for comparisons between two groups. Chi-square was used to compare categorical variables. For all analyses, a significance level of 5 % was used. The data were analyzed using SPSS for Windows version 16 (SPSS, Chicago, IL, USA), except for the analysis comparing SF-36 scores between dialysis patients and population norms (paper I), for which Number Cruncher Statistical System for Windows, 2007 version (NCSS, Kaysville, UT, USA) was used.

Reliability measures of the HRQOL and depression scales

A measurement tool is reliable if it consistently provides the same results every time a specific variable is measured. A common test of reliability includes homogeneity. Homogeneity testing examines the extent to which all the items in a multi-item scale consistently measure a variable. Homogeneity, also called internal consistency, was estimated with the Cronbach´s alpha coefficient (r). A Cronbachs´s alpha coefficient of 1.00 equals perfect reliability, whereas a score of 0.00 indicates no reliability. As recommended by Nunnally (84), a Cronbach's α value of ≥0.70 was used as an indicator of adequate internal consistency. For every scale used in the current sample, Cronbach's α coefficient for the internal reliability test was calculated. The Cronbach's α coefficient values from our study are summarized in Table 1, together with reported values from Denmark and the US (Table 1). Cronbach's α coefficient for the internal reliability test ranged from 0.75 to 0.92 for the eighth generic scales in SF-36. Two of the disease-specific scales had Cronbach's α coefficient of < 0.70 ("work

status"=0.51 and "quality of social interactions"=0.50). The BDI scale had a Cronbach's α coefficient value of 0.87, in the current sample (n=280).

The two scales "quality of social interaction" and "work status" did not reach the recommended Cronbach's α value of 0.70 in a test of data from all patients in our study. The same findings were also reported in the reliability testing of the Dutch version of KDQOL-SF (19). Apart from those two dimensions, our study demonstrate that the internal consistency reliability of the Norwegian version of KDQOL-SF is of the same level as that of the original U.S. English version (59).

Table 1. Internal consistency reliability (Chronbach´s α) of the disease-specific scales of the KDQOL-SF and the generic scales on the SF-36 for dialysis patients

		Cronbach´s α		
Scale	No of items	Danish version[a]	U.S. version[b]	Norwegian version[c]
Disease-specific scales of the KDQOL-SF				
Symptoms and problems	12	0.79	0.84	0.77*
Effects of kidney disease	8	0.71	0.82	0.78
Burden of kidney disease	4	0.85	0.83	0.77
Work status	2	0.72	0.83	0.51
Cognitive function	3	0.81	0.68	0.77
Quality of social interaction	3	0.43	0.61	0.50[§]
Sexual function	2	0.93	0.89	0.90
Sleep	4	0.83	0.90	0.75
Social support	2	0.67	0.89	0.70
Dialysis staff encouragement	2	0.70	0.90	0.75
Generic scales of the SF-36				
Physical function	10	0.93	0.92	0.92
Role limitation due to physical problems	4	0.83	0.87	0.86
Bodily pain	2	0.90	0.90	0.86
General health	5	0.77	0.78	0.75
Vitality	4	0.90	0.90	0.83
Social function	2	0.83	0.87	0.80
Role limitation due to emotional problems	3	0.79	0.86	0.85
Mental health	5	0.89	0.80	0.82

[a]Data reported by Hays et al (59).

[b]Data reported by Molsted et al (78).

[c]Data from Østhus et al.(74).

*Only hemodialysis patients included, for PD patients Cronbach´s α=0.75

[§]Cronbach´s α empowered to 0.60 if item 13e ("Did you get along well with other people?") deleted

Grouping of patients according to age quartiles (paper I)

Anchoring HRQOL measures in population norms makes clinical interpretations of HRQOL in diseased patients, more meaningful (77). Patients were grouped according to age quartiles (18–49, 50–61, 62–72 and 73–89 years) instead of age decades, to enhance the sample size in each group (Figure 6.7). The SF-36 subscale scores of the age quartile groups, were compared with those of appropriate age (by decade)- and gender-matched population norms (77).

Multivariate analysis

In multivariate regression analysis, a mathematical expression is used to relate two or more independent variables to an outcome or dependent variable. Multiple regression analysis is an extension of a simple regression in which an outcome is predicted by a linear combination of two or more predictor variables. In multiple linear regression analysis, the outcome variable is a continuous quantity. A linear regression coefficient indicates the impact of each independent variable on the outcome in the context of (or "adjusting for") all other variables. Continuous skewed variables (dependent and independent) were log-transformed before being entered.

To assess relationships between current smoking, HRQOL and depression (paper I), linear regression analysis was chosen. Log-transformed BDI, log-transformed CDI, PCS and MCS scores were set as dependent variables in separate multivariate models. Current smoking status was set as an independent variable together with all selected covariates. The impact of current smoking status on HRQOL or depression was estimated by its regression coefficient in the context of all other selected covariates. Unstandardized beta values were estimated with 95% confidence intervals (CIs). The interpretations of the beta values (paper I) are difficult, due to log-transformation of dependent variables (BDI and CDI). Yet, it was the association between smoking and HRQOL or depression that was of interest, and whether there are true associations. The magnitude of explained variance can be depicted by the R^2 values given for the different models.

Confounding and selection of covariates (Paper I - III)

A confounding variable can be defined as a variable other that the predictor variable in which we are interested, that potentially could affect the

outcome variable. Thus, a potential confounder should be associated with both the dependent and the independent variable in a regression analysis. Thorough selection strategies for potential confounders (independent covariates) were done. Each independent variable was evaluated for its association with the dependent variable (bivariate confirmation). Demographic and clinical variables were selected from bivariate analysis if they were correlated ($p < 0.2$) with both current smoking and the dependent variable, or if they were considered clinically important. The significance level was set to 0.2 to avoid losing important factors.

Multicollinarity occurs when the independent variables in the multiple regression equation are strongly linearly correlated. With high correlation between independent variables, the quantitative risk estimate for each variable maybe imprecise and difficult to interpret (85). Therefore strict criteria were followed in the selection process of independent variables. If Spearman's correlation coefficient between two potential confounders was outside the interval – 0.70 to 0.70, one of them was excluded (paper I-III). Additionally, to avoid that multicollinarity would bias the regression models, variance inflating factors (VIF) were computed for the covariates participating in multivariate analysis (Paper I). The VIF is a measure of multicollinearity. A VIF value of >10 is a good reason to worry (86). The maximum VIF value for a participating covariate was 1.92 (paper I). Backwards variable selection was then applied to identify the most important covariates that remained in the final models (Paper I-III).

Logistic multivariate analysis (Paper II)

In multiple logistic regression analysis, the dependent variable is a dichotomous quantity. The risk estimate on the outcome from each independent variable in the model is depicted by odds ratio (OR). Multivariate logistic regression models were created to investigate the relationship between acceptance status for RTX, HRQOL and depression.

Acceptance status (dichotomized into yes/no) was set as dependent variable. MCS, PCS, and BDI scores were set as independent variables in three separate regression models. ORs depicting the relationships between HRQOL and depression with acceptance status for RTX were calculated. Selection of covariates to the regression models was done in similar way as in Paper I.

Finally a unique multivariate hierarchical regression model was created, to see how the ORs changed if different sets of independent variables were added to the model (paper II). Both the PCS and BDI were included in this analysis simultaneously. MCS was let out due to lack of association with the dependent variable of interest (acceptance status for RTX). No significant interaction between the PCS and the BDI score were observed. An interaction occurs between independent variables if the impact of one variable on the outcome depends on the level of another variable. The presence of significant interaction between two independent variables in a multivariate model could bias the risk estimates (ORs).

To investigate whether HRQOL or depression could predict the likelihood of receiving a renal transplant, Cox regression analysis was applied. In proportional hazard regression, also known as Cox regression (85), the outcome variable is the duration of time to the occurrence of a binary event during a follow-up period of observation. Time from study participation (time zero) until renal transplantation (event) was the dependent variable (time to event). Each patient´s final state at end of follow-up could be classified as either transplanted at a specific time or as censored if lost to follow up or not transplanted (still in dialysis) by the end of follow up. Patients were also censored by time of death. Censoring is a technique for incorporating differing lengths of patient follow-up from a longitudinal study. The censored patients contribute information only until the time that they leave the study. The unadjusted and multi adjusted hazard ratios for transplantation during follow-up per unit increase in HRQOL or BDI score were estimated with 95% CI.

Overfitting

The hazard ratio may be unreliable if the multivariable data contain too few outcome events (transplantation), relative to the number of independent variables. In general, the results of models having fewer than 10 outcome events per independent variable are thought to have questionable accuracy (87). Of the 86 patients with pending transplantation status at study start, 47 events (transplantations) occurred during follow up (paper II).

Estimating HRQOL quartile scores (Paper III)

HRQOL component summary scores (PCS-36, MCS-36, PCS-12 and MCS-12) were divided into quartiles (paper III). Kaplan-Meier curves, with

log-rank tests, were applied to compare survival rates between groups with different HRQOL quartile scores. Although HRQOL is considered a continuous variable, we implemented quartiles to reveal clinically significant differences. By comparing quartiles, information that may be of clinical relevance may emerge more clearly. Lectures by Hosmer DW emphasized the utility of applying quartiles (even though symmetrical distributed) to get information from the data that may be of clinical interest (oral communication from Professor Leiv Sandvik).

Cox proportional hazard models, were used to estimate the unadjusted and adjusted hazard ratios (HRs) of death for groups with different HRQOL quartile scores, and for changes in continuous HRQOL scales by one-unit increments (paper III). HRs are presented with 95% confidence intervals. In quartile analyses, the upper quartile (best perceived state) was used as the reference level. Demographic and clinical variables listed in Table 1 were set as independent variables in separate univariate Cox regression analyses to identify variables significantly associated with death; variables with $p < 0.2$ were entered into the adjusted Cox regression model as covariates. Furthermore, a potential confounder must also be associated with the independent variables of interest (PCS-36, MCS-36 and BDI were chosen). Thus, the selection of covariates in multivariate Cox-regression analysis followed the same strategy as in linear and logistic multivariate regression analysis (paper I and II).

Results of the papers

Paper I

Overall, both male and female dialysis patients scored significantly lower than the Norwegian population norms on all SF-36 subscales. After stratification for age quartiles, the differences between dialysis patients and the general population were attenuated with increasing age. In the two highest age-quartiles, female patients scored better than males on some SF-36 scales relative to normative data. In female dialysis patients above 72 years all SF-36 subscales were similar to the norms except the general health perception (Table 2A). While male patients above 72 years scored significantly poorer on seven of eighth SF-36 subscales compared with the respective norms (Table 2B). Complete datasets of all age groups and of both gender were not given in paper I, and are therefore reported here (Table 2A and 2B).

The mean BDI score for the study patients (n=280) was 11.4±7.9, and the median score was 10.0 (Q_1 6.0, Q_2 15.5). In this study, patients below the median age of 62 years scored higher on the BDI that those above (11.5 (Q_1 6.0, Q_3 18.0) vs. 9.0 (Q_1 6.0, Q_3 14.0), p = 0.024), and the prevalence of depression was also higher in the youngest group (41.1 % vs. 25.2%, p = 0.005). The prevalence of depression, defined as a total BDI score above 14, was 33.2%, and differed significantly between smokers and non-smokers (52.8 vs. 26.4%, p < 0.001).The PCS score was equally compromised in smokers and non-smokers (37.2±10.4 vs. 35.7±10.2, ns.). MCS was significantly reduced in smokers compared with non-smokers (44.1 ± 12.2 vs. 48.7 ± 10.3, p < 0.001).

Current smoking was independently associated with higher BDI score (data log-transformed, unstandardized ß = 0.156, CI 0.008 to 0.305, p = 0.039, adjusted R^2 = 0.505), as well as with higher CDI score (log-transformed, unstandardized ß = 0.146, CI 0.046 to 2.46, p = 0.005, adjusted R^2 = 0.495) and worse score on MCS (unstandardized ß = -4.622, CI -7.544 to -1.699, p = 0.002), after adjustments for multiple covariates.

Table 2A. SF-36 subscale scores in female dialysis patients compared with age-matched females from the general population

SF-36 subscale	Female dialysis patients	Female reference population*	T-test p -value
	Age: 18 – 49 years (n= 32)	40 – 49 years (n=225)	
PF	64.4 ± 27.5	88.7 ±17.2	<0.0001
RP	35.8 ± 38.7	83.0 ± 32.9	<0.0001
BP	56.6 ± 30.1	74.4 ± 26.3	<0.001
GH	43.1 ±24.6	79.3 ± 22.9	<0.0001
VT	43.1 ±24.5	58.5 ±21.5	<0.001
SF	67.3 ±28.1	85.7 ±24.7	<0.001
RE	66.7 ± 42.0	84.1 ± 30.7	<0.001
MH	70.5 ±18.9	77.9 ±18.4	<0.05
	Age: 50 – 61 years (n=25)	50 – 59 years (n= 181)	
PF	41.2 ± 27.4	85.6 ± 16.6	<0.0001
RP	48.0 ± 44.2	77.6 ± 36.2	<0.001
BP	48.0 ± 30.0	73.8 ± 27.1	<0.0001
GH	32.1 ±20.0	74.7 ± 22.4	<0.0001
VT	34.8 ±24.6	62.0 ± 21.0	<0.0001
SF	62.0 ±27.4	86.0 ± 21.3	<0.0001
RE	48.0 ± 44.2	84.3 ± 30.9	<0.0001
MH	67.4 ±19.8	79.5 ± 17.3	<0.01
	Age: 62 – 72 years (n=19)	60-69 years (n= 152)	
PF	45.0 ± 28.0	70.5 ± 23.3	<0.0001
RP	29.2 ± 43.1	55.3 ± 43.3	<0.05
BP	48.9 ± 35.7	62.6 ± 27.8	Ns
GH	37.9 ±27.3	63.1 ± 25.1	<0.0001
VT	45.0 ±23.3	55.4 ± 22.8	Ns
SF	67.1 ±30.4	81.5 ± 22.7	<0.05
RE	64.8 ± 43.5	74.5 ± 38.5	Ns
MH	74.7 ±21.0	77.9 ± 17.8	Ns
	Age: 73 – 89 years (n=26)	>70 years (n=117)	
PH	44.4 ± 25.9	56.1 ± 27.8	Ns
RP	30.0 ± 42.1	37.0 ± 43.0	Ns
BP	55.2 ± 31.4	59.5 ± 29.0	Ns
GH	52.1 ±21.0	62.5 ± 22.1	<0.05
VT	48.9 ±24.0	50.6 ± 22.9	Ns
SF	65.9 ±28.0	74.1 ± 28.7	Ns
RE	49.3 ± 46.2	59.5± 44.2	Ns
MH	78.7 ±18.7	76.7 ±17.8	Ns

Abbreviations: PF= Physical function, RP= Role limitation due to physical problems, BP= Bodily pain, GH= General health, VT= Vitality, SF= Social function, RE= role limitation due to emotional problems and MH= Mental health.

*Normative data published by Loge et al (77)

Table 2B. SF-36 subscale scores in male dialysis patients compared with age-matched males from the general population

SF-36 subscale	Male dialysis patients	Male reference population*	T-test p -value
	Age: 18 – 49 years (n= 42)	40 – 49 years (n=220)	
PF	72.2 ± 22.8	91.9 ± 12.3	<0.0001
RP	34.6 ± 39.7	86.4 ± 28.7	<0.0001
BP	61.5 ± 27.0	78.9 ± 25.5	<0.0001
GH	41.9 ±20.9	79.3 ± 21.2	<0.0001
VT	43.9 ±21.2	65.4 ± 21.9	<0.0001
SF	64.0 ±32.0	87.6 ± 20.9	<0.0001
RE	61.0 ± 41.4	89.2 ± 26.0	<0.0001
MH	72.8 ±19.1	80.6 ± 15.8	<0.01
	Age: 50 – 61 years (n=48)	50 – 59 years (n= 181)	
PF	54.0 ± 28.0	87.2 ± 17.4	<0.0001
RP	25.0 ±38.6	78.0 ± 35.9	<0.0001
BP	55.0 ± 28.6	73.2 ± 25.5	<0.0001
GH	41.3 ±21.2	74.1 ± 22.5	<0.0001
VT	45.3 ±19.4	62.4 ± 21.6	<0.0001
SF	62.0 ±33.1	86.5 ± 24.1	<0.0001
RE	52.1 ±45.6	87.5 ± 27.9	<0.0001
MH	72.3 ±20.4	79.7 ± 16.0	<0.01
	Age: 62 – 72 years (n=57)	60-69 years (n= 131)	
PF	60.3 ± 25.1	84.3 ± 16.9	<0.0001
RP	25.6 ± 34.6	68.1 ± 43.8	<0.0001
BP	65.7 ± 25.6	70.6 ± 25.4	Ns
GH	46.3 ±23.3	68.0 ± 25.1	<0.0001
VT	43.9 ±22.4	64.7 ± 21.6	<0.0001
SF	68.0 ±24.1	89.3 ± 20.2	<0.0001
RE	57.6 ±42.5	78.6 ± 31.9	<0.001
MH	78.1 ±17.6	81.2 ± 15.8	Ns
	Age: 73 – 89 years (n=52)	>70 years (n=110)	
PH	42.8 ± 25.9	75.0 ± 19.8	<0.0001
RP	13.1 ± 24.1	52.5 ± 43.8	<0.0001
BP	57.7 ± 23.7	69.4 ± 27.4	<0.01
GH	45.7 ±19.0	67.5 ± 22.6	<0.0001
VT	44.7 ±18.9	61.9 ± 21.8	<0.0001
SF	69.7 ±24.7	82.3 ± 23.8	<0.01
RE	40.7 ± 40.6	69.7 ± 37.6	<0.001
MH	77.9 ±13.0	82.7 ± 16.9	Ns

Abbreviations: PF= Physical function, RP= Role limitation due to physical problems, BP= Bodily pain, GH= General health, VT= Vitality, SF= Social function, RE= role limitation
due to emotional problems and MH= Mental health.
*Normative data published by Loge et al (77)

Paper II

HRQOL and depression in chronic dialysis patients accepted (RTX+, n=122) or rejected (RTX-, n=93) for renal transplantation (RTX) were compared. Dialysis patients with pending acceptance status (RTX±, n=86) were followed for a median time of 3.6 (range 2.8 – 4.5) years to assess whether HRQOL or depression predicted the likelihood of receiving a transplant.

The prevalence of depression (defined as a BDI score $\geq$15), and the level of depressive symptoms (BDI score), were similar in the three patient groups (RTX+: 29.1 % depression, median BDI score: 9.0 (IQR; 5.0-15.3), RTX±: 28.8 %, BDI score: 10.0 (6.0-16.8), and RTX-: 32.5 %, BDI score 10.0 (7.0-15.5). While patients rejected for RTX had significantly poorer PCS score compared to patients accepted or patients with pending acceptance status (RTX+: 40.4 ± 10.1, RTX±: 36.5±10.0, RTX-: 32.4±9.4, $p<0.001$), the MCS score was similar in the three groups (RTX+: 48.0 ± 11.1, RTX±: 46.5±11.8, RTX-: 47.9±9.8, p=ns).

However, in multivariate analysis (including patients accepted or rejected for RTX), a significant association between reduced BDI score (less depressive symptoms) and being accepted for RTX emerged. The association between higher PCS score (better perceived physical health) with being accepted for RTX persisted in multivariate analysis. No association between acceptance status and MCS was observed. Less depression and better HRQOL (PCS) were associated with being on the waiting list for RTX after adjusting for comorbidity, age, gender and dialysis vintage.

During follow-up, 55 % (n=47) of the dialysis patients in the group with pending acceptance were transplanted. The likelihood of receiving a renal graft during follow-up in patients with pending acceptance status, was not influenced by PCS (adjusted HR 1.01, 95% CI 0.98 – 1.04), MCS (adjusted HR 1.00, CI 0.97 – 1.03), or BDI (adjusted HR 1.00, CI 0.96 – 1.05) score, after adjustment for age, gender, comorbidity and log-transformed dialysis vintage. Only comorbidity remained an independent predictor for receiving a renal transplant.

Paper III

Whether HRQOL measured with SF-12 or SF-36 component summary scores predicted mortality in dialysis patients was assessed after a median follow-up of 3.6 years (range 2.8 to 4.5 years). Of the 301 study patients, 21 patients were excluded from survival analysis due to short observation time (< 2 months). Ten patients missed the SF-36 component summary score and additionally 18 patients missed the SF-12 component scores, thus data from 252 patients were analyzed. At end of follow-up 85 patients (33.7 %) had died and 122 patients (48.4 %) had received a renal transplant. The most frequent causes of death were cardiovascular disease 42.4% (n=36), sepsis 31.8% (n=27), and malignant disease 14.1% (n= 12). Significant correlations were observed between PCS-36 and PCS-12 (ρ= 0.93, p<0.001, n=252) and between MCS-36 and MCS-12 (ρ=0.95, p<0.001, n=252).

Compromised PCS-36 was associated with higher age, longer dialysis vintage, lower serum albumin, and higher comorbidity score. While reduced MCS-36 was associated with younger age, current smoking, and being unable to work due to health. In univariate analyses, increased mortality was significantly associated with higher age, higher comorbidity score, current smoking, and longer log-transformed dialysis vintage. No associations with dialysis modality, gender, hemoglobin, previous graft failure, serum albumin, body mass index, or cholesterol were observed.

Kaplan-Meier curves showed higher mortality rates for patients in the lowest quartiles of PCS-12 (χ^2 = 15.3, p=0.002) and PCS-36 (χ^2 = 16.7, p=0.001). No association between MCS (neither MCS-12 nor MCS-36) and mortality was observed.

During follow-up, patients with the lowest PCS-12 quartile score had a 2.5-fold higher risk of death compared to patients in the highest quartile (best perceived state) after adjusting for age, gender, log-transformed dialysis vintage, comorbidity score and albumin. For the PCS-36 quartiles, the corresponding difference in risk was 2.7 after multiple adjustments.

Discussion

Methodological considerations

Study design

In order to study prevalence's of HRQOL, depression, clinical and sociodemographic characteristics in prevalent dialysis patients, a cross-sectional design was used. An obvious limitation is that we cannot conclude about causality. The results from the present study may serve as reference data for future research.

Bias

In a broad perspective, bias may be defined as any factor or process, which tends to produce results or conclusions that differ systematically from the truth. More specifically, selection bias occurs when participants in a study differ in a systematic way from the background population.

Due to the inclusion criteria in the present study, patients with cognitive impairment, psychosis and drug abuse could not be included. Furthermore, it was a clinical impression during data collection that those patients willing to participate in the study presented as healthier than patients refusing. The most common reasons for refusing participation were exhaustion and lack of motivation. Lack of motivation can also be a symptom of depression. Thus, our results concerning HRQOL and depression may be an underestimation due to non-response bias.

Information bias

Answers on questionnaires may be a source of information bias. Patients have a tendency to under-report number of daily smoked cigarettes, because the question may be perceived as value-laden. In our study (paper I) patients were classified as smokers or non-smokers, and differences in HRQOL and depression scores were prominent.

Internal and external validity of the questionnaires

The Cronbach's α coefficient for the internal validity was estimated for all scales used in the current work. Two of the scales ("quality of social interaction" and "work status") from the KDQOL-SF did not reach the recommended level of >0.70 in our data. In accordance with data from US(59), Denmark (78), the Netherlands (19) and Japan (88), the scale "quality of social interaction" did not reach the recommended value of >0.70 . Similarly to the Danish(78) report, the Cronbach's α value was empowered to 0.60 if one of the three items was deleted from the scale (Table 1). Also the "work status" scale had a Cronbach's α coefficient score below 0.70 in our data, similar to the Dutch version(19). However, overall, the internal validity was high (Table 1), supporting the reliability of the instruments used in this cohort of Norwegian dialysis patients. Also the distribution curve of BDI in our sample was similar to what has been reported in data from the US (89), supporting the validity of this instrument within our cohort.

Our study was carried out in a culturally homogeneous group, as only seven of 301 patients were non-Caucasians. The Norwegian dialysis patients are characterized by high transplantation rate and thus short time in dialysis than what patients from other countries may experience. Our results can therefore not necessarily be applied on other populations.

Case mix

Case-mixing may create a problem in HRQOL studies (45;90). This is adjusted for in the statistical analyses.

Completeness of data

Efforts were made during the data collection to enhance completeness of data. Thus, the KDQOL- SF questionnaire was complete for more than 90.0% of all scale scores, except for two scales "sexual function" and "dialysis staff encouragement" for which 55.2 % and 83.4 % were complete.

In SF-36 questionnaires, if there were missing data in half or less than half of the items within a scale, the missing values were replaced with the

respondent's mean score across the completed items in the same scale (77). The SF-36 was initially scored without substituting missing items, and a total of 284 (94%) component summary scores could be calculated. When applying the algorithm including substitution of missed items (if $\leq$ 50% missing items within the scale, the missing value was substituted by the mean of the other item scores within the same scale in the same patient) the number of component summary scores was empowered to 291 (97%). The substituted SF-36 scale scores are presented (paper I, II and III). When estimating component summary scores, all eight subscales on the SF-36 had to be included. Thus, the substitution was only done when scoring at subscale level. The percentages of missing scale scores on the SF-36 after substitution ranged from 1.0 % for physical function and bodily pain, to 2.3% on the role limitation due to emotional problems, resulting in 291 physical and mental component summary scores.

When scoring the SF-12 component summary scores (PCS-12, MCS-12, paper III), no substitution was made. The summary scores (SF-12) were estimated directly from the 12 items, thus a total of 284 (94%) SF-12 component summary scores were calculated (http://gim.med.ucla.edu/kdqol/downloads).

The BDI was complete on all items in 237 patients (79%). If less than five items of the 21 items in the BDI were missing, these were substituted by the most frequent occurring item score from the rest of the study sample. If more than 5 items were missing, the patient was excluded. BDI could thus be scored in 280 patients (93%).

For the kidney specific scales in KDQOL, no substitution for missing item values was done. Numbers of complete scale scores (KDQOL-SF, BDI) are given in parenthesis in the Tables (paper II and paper III).

Selection of study instruments (questionnaires)

Patient-reported measures are a core aspect of health care. But there is much to learn about how to use HRQOL instruments in order to improve clinical practice (91). In the early nineties it was forecasted that HRQOL

questionnaires would become methodologically more sophisticated as well as simpler to use and interpret in near future (17). The KDQOL-SF instrument is designed to assess psychological and treatment related problems specific to patients in dialysis (50). The present study we assessed HRQOL according to the present recommended procedures by applying the KDQOL-SF version 1.3 including both generic and disease specific dimensions (19). In that manner our results could be compared with normative data from the general Norwegian population(77), as well as specific kidney related problems could be assessed. Additionally we used the SF-12, to assess if this short 12-item questionnaire would perform similarly to the longer version SF-36 with regard to predict mortality.

Discussion of the results

Paper I

Our results show that HRQOL is compromised and clinical significant symptoms of depression prevalent in Norwegian dialysis patients. Overall, both male and female dialysis patients scored significantly lower on all SF-36 subscales compared with age- and gender-matched norms (paper I). The observation that mental aspects of HRQOL were more suppressed compared to the age-matched general population in the youngest age groups, may reflect that younger patients are more vulnerable as they have higher expectations with regard to health than elderly. The younger patients were also more likely to smoke than elderly patients. We observed that smokers had reduced mental health (MCS score) and more depression than nonsmokers. The reciprocal relationship between smoking and depression is well documented in epidemiological studies (70;92). Our study demonstrates this relationship in dialysis patients, as the associations between smoking and depression or poor MCS persisted after multiple adjustments. In a regression model with CDI score as dependent variable (CDI: a scale evaluating depressive symptoms without including somatic symptoms of depression), current smoking, younger age, lower education, being divorced/separated, higher comorbidity and poorer scores on effect of kidney disease, social support, sleep and symptoms were all independently associated with higher CDI score (more depression).

PCS was not worse in smokers vs. non-smokers (37.1±10.4 vs. 35.7±10.2, ns), but still both groups had very poor scores. In comparison, an average PCS score of 52.9 has been reported for Norwegian general population with no self-reported medical condition (44). Contrary to our findings, a recent Danish study including 71 HD and 59 PD patients, found that smoking had an independent negative effect on the PCS, while no association with MCS was found (71). The authors concluded that physical activity should be encouraged, and that information on health effects of smoking and quitting smoking techniques should be a natural part of the treatment (71).

Studies assessing non-adherence among dialysis patients have observed that up to 60% of dialysis patients do not adhere to neither diet, fluid-intake nor medication regimen (93). Compliance to medical treatment is of crucial importance for outcome in ESRD patients(94), since these patients depend on multiple drugs and extensive treatment regime. Our results that negative health behavior like smoking is associated with depression and poor mental health, could suggest a need to identify and treat depression in order to cope with smoking cessation. If considering smoking as a sign of non-compliance, or as a maladaptive coping strategy to experienced loss and burden, well-targeted interventions (depression screening and treatment, and/or smoking cessation programs) seem clinical meaningful. Based on our results we may hypothesize that if depression is alleviated, patients would be better enabled to make better decisions on lifestyle changes. As smoking is a known risk factor for cardiovascular disease in ESRD patients, smoking cessation is of great importance to these patients. Our study was cross-sectional, and causality cannot be concluded. Clinical intervention studies assessing whether treatment of depression may ease smoking cessation in dialysis patients is needed.

Paper II

Being accepted for RTX was associated with higher PCS score and fewer depressive symptoms. It is known that renal transplantation is a superior alternative to dialysis for ESRD patients (95). Thus, we may interpret our findings that knowing that transplantation is a realistic option has a positive effect on patient's self- perceived HRQOL. We may think that future perspectives of better health itself may affect HRQOL positively. This is in line with the hypothesis raised by Perneger et al (50), that being accepted

for RTX “per se” could affect HRQOL positively. A recent paper published after we had reported our data, confirms our findings that fewer depressive symptoms and better HRQOL are associated with being on the waiting list for RTX in ESRD patients(96). The latter observation was based on 6383 prevalent HD patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS)(96). The authors conclude though, that low subjective well-being may identify patients with reduced access to the waiting list. And they speculate that patients with compromised HRQOL are less likely to get access to the transplantation program (96). A causal relationship between HRQOL, depression and acceptance status for RTX, can only be answered in well-designed longitudinal studies, in which HRQOL data are measured repeatedly from the first nephrology referral and planning of RRT to acceptance for renal transplantation.

Patients with chronic illness adapt to the disease and the consequences with time, even with preserved mental aspects of HRQOL. Evidence has suggested that psychological distress increases as time on the waiting-list for RTX increases (97), and decreases after RTX (98). How time on the waiting list can affect HRQOL and prevalence of depression should be addressed in future longitudinal studies.

In the prospective part of this study including 86 prevalent dialysis patients with pending acceptance status for RTX neither HRQOL nor depression had any effect on the likelihood of receiving a transplant. Only comorbidity was an important contributing factor; low comorbidity score predicted increased likelihood for RTX, which would be expected. These findings are reassuring with regard to the present clinical practice in Norway, implicating that all patients have similar possibilities to be transplanted, and only objective criteria, e.g. cardiovascular health, limit the possibility. The eligibility for RTX is based on medical factors, and the pre-requisite for organ allocation based on ABO and HLA-matching. Thus our findings contradict previous reports indicating that non-medical factors like gender or psychosocial variables limits the access to waiting list and RTX (99-102). In the recent DOPPS study (96), prevalent waitlisted HD patients (n=1838) were followed for approximately 1.5 year, and time of RTX registered. Similarly to our results, the likelihood of receiving a renal transplant was not predicted by HRQOL or depression. However, it was observed gender and ethnicity differences; the transplantation rate was lower among females and blacks.

In Norway, female gender does not limit the possibility for RTX(13), and transplantation in elderly is encouraged (14).

Only patients with pending transplantation status at baseline were included in our prospective Cox analysis with regard to likelihood of receiving a RTX. This contrasts the DOPPS study (96). Patients already on the waiting list were included in the prospective analysis. When patients are placed on the waiting list, it is expected that they eventually will be transplanted, therefore, the best way to demonstrate whether psychosocial factors have impact on the probability for RTX would be in patients with pending status for being on the waiting list.

Finally, the finding that poor HRQOL, as measured with PCS and higher level of depressive symptoms were associated with being permanently rejected for RTX should draw attention to the clinical challenges posed by that decision. How can clinicians offer optimal medical care to patients permanently rejected for RTX, and facing life-long dialysis? How can HRQOL be improved or at least maintained? Clinical depression should be focused on in patients rejected for RTX.

Paper III

HRQOL measured with the PCS is an independent predictor of mortality in dialysis patients, whether using the short (PCS-12) or the full-length (PCS-36) version of the SF-36 questionnaire.

Our data has shown that the PCS-12 is a strong and independent predictor of death in dialysis patients during a median follow-up of 3.6 years. The different mortality rates between the PCS-12 quartiles (n=252) diverged step-wise (Kaplan-Meier plots, paper III). Patients in the 3rd PCS-12 quartile had 1.7 higher multi-adjusted hazard ratio of death, and patients in the 2nd PCS-12 quartile had a 2.4 higher multi-adjusted hazard of death compared with the highest quartile (best perceived state) during follow-up. Patients in the lowest PCS-12 quartile had a 2.5 higher hazard ratio of death during follow-up, compared with those in the highest quartile after adjusting for age, gender, comorbidity score, dialysis vintage and albumin. The questionnaire (SF-12) is easy to fill out (it consist of 12 items), and not very

time consuming. Based on our result, we suggests that the PCS-12 score (from SF-12) could be used repeatedly as a risk estimate in dialysis patients, just as the level of serum albumin is measured monthly. Based on our findings, SF-12 seems to be a valid tool for risk estimation in dialysis patients. Previous studies have compared the predicative effect of HRQOL on mortality with the traditional risk factor albumin, and in the large DOPPS study, it was observed that a 10-point lower PCS score (based on the SF-36) was associated with increases in the risks of death and hospitalization that were greater than the corresponding increases in the risks associated with 1 g/dL (10 g/L) lower serum albumin level (24). In our study we adjusted for albumin in the multivariate analysis.

The MCS-12 or the MCS-36 did not affect mortality in our data. In general, the reduction of HRQOL scores with norms in ESRD patients is greater for physical than for mental health (27;103). It has been suggested, that the impact of chronic disease on aspects of self-assessed mental health may become blunted with time, due to psychological adaptation (40). In this perspective, it may be that when studying prevalent dialysis patients, the effect of MCS on mortality could be blunted. Based on present literature, we would expect that both presence of depression or high level of depressive symptoms as measured by the BDI, as well as poor MCS score from SF-36, potentially could have negative impact on survival in dialysis patients. In a study of 294 ESRD patients treated with HD, Kimmel et al reported that, the level of depressive affect measured by the BDI was significantly associated with mortality, when depression was treated as a time-varying covariate based on periodic follow-up assessments and using multiple, pooled measurements of depression (89). While, patients´ baseline level of depression was not a significant predictor of mortality at 38.6 months of follow-up (89), in accordance with our present findings. Similarly, in a more recent study, Boulware et al. (104) assessed data from the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) study, a large observational follow-up study in the US, levels of depression at the beginning of the study was not associated with increased overall mortality risk, but with several different time-dependent analyses they could confirm that persistently high levels of depressive affect over time were associated with death (104). In our study, we were limited to study associations between self-assessed mental health at study inclusion, with survival after a median follow-up of 3.6 years. Longitudinal studies with repetitive measurements of HRQOL and depression should be done, in order to understand mechanisms underlying the relationship between depression

and survival, and the effect of treatment of depression in dialysis patients. It also emphasizes the importance of repeatedly using questionnaires to identify HRQOL and depressive symptoms in dialysis patients in order to intervene in high-risk individuals.

Conclusions

- Reduced HRQOL and high level of depressive symptoms are present in Norwegian dialysis patients (paper I).

- Poor mental health and higher level of depressive symptoms are associated with current smoking in chronic dialysis patients (paper I).

- Compromised HRQOL and higher level of depressive symptoms are associated with being rejected for RTX in dialysis patients (paper II).

- The HRQOL and level of depressive symptoms did not predict the likelihood of RTX in dialysis patients. Only the comorbidity had impact on probability of RTX (paper II).

- HRQOL strongly predicts mortality in patients on chronic dialysis, after adjustments for traditional risk factors. The PCS score from the SF-36 provided comparable results as the PCS score from the shorter SF-12 (paper III).

Clinical implications of thesis

- Our finding that HRQOL is substantially suppressed in Norwegian dialysis patients relative to normative data from the general population, point to the urgent need to increase and possible improve supportive care to this growing patient population.

- Our results highlight the importance of routinely HRQOL assessments in clinical practice. HRQOL measurements are important in order to gain information about clinical status and well-being, and to identify patients at risk of poor outcome. The assessments can enable adjustment of care according to individual patients needs.

- Our finding that younger dialysis patients are more susceptible for depression than older patients, should aware clinicians that different sub-groups of patients may have different needs regarding symptom assessment and treatment.

- Routinely screening for depression in dialysis patients is needed, in order to identify patients that may have benefit on other types of treatment. Inter-disciplinary cooperation between nephrologists and consultation-liaison psychiatrists should be encouraged.

- Because the SF-12 requires less time to complete than the SF-36, it could be a feasible instrument to apply in routinely HRQOL assessments, in addition to other, more traditional, risk factors. We suggest the PCS-12 to be assessed regularly in dialysis patients.

- Physical exercise programs in dialysis should be encouraged, as the physical aspects of HRQOL (PCS) were so substantially suppressed in our study. There are no such offers for dialysis patients in Norway, contrary to patients with chronic pulmonary diseases and cancer patients. There is no reason that ESRD patients should be left in physical inactivity.

Future research

Not only do we need easily accessible tools to diagnose reduced HRQOL and estimate risk, but also we need to know more about treatment options in a particularly vulnerable patient group characterized by high comorbidity. We do not only need longitudinal study on HRQOL and depression in dialysis patients, but also randomized controlled trials of therapy aimed at modifiable risk factors such reduced mental health and low HRQOL. We need to highlight causality rather than associations as many researchers previously have pointed out. Be that as it may, it is important to assess how patients adapt to ESRD during time, and to identify possible vulnerable phases where patients may be in need of enhanced supportive care. Our prevalent data cannot give information about that.

Suggestions for future research based on the thesis:

- Regular and repeated assessment of HRQOL in incident dialysis patients in order to assess how HRQOL evolves during time.
- Clinical intervention studies to investigate whether treatment of depression may improve HRQOL and ease smoking cessation in dialysis patients.
- Follow-up studies to investigate whether RTX translates into further improvement of HRQOL and less depression.
- Assess whether time on the waiting list can affect HRQOL and prevalence of depression in dialysis patients.
- Follow-up studies assessing the impact of depression and impaired HRQOL on graft survival after RTX, and whether graft function will affect HRQOL.
- To describe HRQOL in different subgroups of dialysis patients, to identify patients at particular risk of compromised HRQOL.
- Longitudinal studies with repetitive measurements of depression, in order to understand mechanisms underlying the relationship between depression and survival.
- Controlled clinical trails to assess if physical training programs would improve the physical composite scores of either SF-12 or SF-36.

Summary of thesis

The current study has demonstrated that HRQOL in Norwegian dialysis patients was significantly poorer than in the general population, and that the prevalence of clinical significant symptoms of depression was high. Compromised HRQOL and high level of depression were particularly prominent in the youngest age group (patients from 18 to 62 years). Current smoking was associated with reduced mental aspects of HRQOL and more depression. While, physical health was equally compromised in smokers and non-smokers. Patients on the waiting list for renal transplantation reported better physical HRQOL and less depression than patients rejected for renal transplantation, irrespectively of comorbidity and age. The likelihood of receiving a renal transplant in Norwegian dialysis patients was not predicted by psychosocial factors, but by the level of comorbidity. Reduced self-reported HRQOL is a strong and independent predictor of mortality in Norwegian dialysis patients. The results from our study highlight that reduced HRQOL and high prevalence of depression in dialysis patients cannot be ignored in clinical practice, and that both issues should be addressed in proper intervention clinical trials, as potential modifiable risk factors.

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Erratum list

In final proofing of Paper III, following corrections was executed:

Correction 1:
In the title a c was changed to a capital C. Correct tiltle: Mortality and health-related quality of life in prevalent dialysis patients: Comparison between 12-items and 36-items short-form health survey

Correction 2:

Table 1,

Range: 9.6 - 30.1 was changed to 9.6 - 30.0
Range: 44.4 - 58.2 was changed to 44.5 - 58.2

I

II

III

HEALTH AND QUALITY OF LIFE OUTCOMES

RESEARCH Open Access

Mortality and health-related quality of life in prevalent dialysis patients: Comparison between 12-items and 36-items short-form health survey

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Abstract

Background: To assess health- related quality of life (HRQOL) with SF-12 and SF-36 and compare their abilities to predict mortality in chronic dialysis patients, after adjusting for traditional risk factors.

Methods: The Short-Form Health Survey (SF-36) with the embedded SF-12 was applied in 301 dialysis patients cross-sectionally. Physical and mental component summary (PCS-36, MCS-36, PCS-12, and MCS-12) scores were calculated. Clinical and demographic data were collected. Mortality (followed for up to 4.5 years) was analyzed with Kaplan Meier plots and Cox proportional hazards, after censoring for renal transplantation. Exclusion factors were observation time <2 months (n = 21) and missing component summary scores (n = 10 for SF-36; n = 28 for SF-12), thus 252 patient were included in the analyses.

Results: In 252 patients (60.2 ± 15.5 years, 65.9% males, dialysis vintage 9.0, IQR 5.0-23.0 months), mortality during follow-up was 33.7%.(85 deaths). Significant correlations were observed between PCS-36 and PCS-12 ($\rho = 0.93$, $p < 0.001$) and between MCS-36 and MCS-12 ($\rho = 0.95$, $p < 0.001$). Mortality rate was highest in patients in the lowest quartile of PCS-12 ($\chi^2 = 15.3$, $p = 0.002$) and PCS-36 ($\chi^2 = 16.7$, $p = 0.001$). MCS was not associated with mortality. Adjusted hazard ratios for mortality were 2.5 (95% CI 1.0-6.3, PCS-12) and 2.7 (1.1 – 6.4, PCS-36) for the lowest compared with the highest ("best perceived") quartile of PCS.

Conclusion: Compromised HRQOL is an independent predictor of poor outcome in dialysis patients. The SF-12 provided similar predictions of mortality as SF-36, and may serve as an applicable clinical tool because it requires less time to complete.

Keywords: Chronic kidney disease, Dialysis, Health-related quality of life, Mortality, Physical component summary score, SF-12 and SF-36

Introduction

Despite advances in dialysis treatment and improvements in the management of traditional cardiovascular risk factors, mortality rates for patients with end-stage renal disease (ESRD) on chronic dialysis remain unacceptably high. For patients with ESRD in Europe and the United States, survival rates after initiation of dialysis treatment are 81.1% and 80.4%, respectively, at one year and 38.2% and 35.8%, respectively, after five years [1,2]. The established predictors of mortality in patients on dialysis include low serum albumin [3], hemoglobin [4], and increasing age [5]. In addition, patients rejected for renal transplantation are at special risk for lethal outcome [6]. Studies have suggested that high mortality rates might be reduced by improving the quality of dialysis, control of phosphates, normalization of serum albumin, and correction of renal anemia [7-9]. However, despite data that indicates that these quality measures in dialysis are improving, mortality rates have not improved in parallel [10].

Recent studies have suggested that a poor health-related quality of life (HRQOL) was strongly related to increased risk of mortality in patients on dialysis [11-17]. Thus,

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although HRQOL is typically used to gain information about patient well-being, it may also indicate the risk of important outcomes, like death.

The medical outcome survey Short Form 36 (SF-36) has been widely used and validated as an HRQOL assessment tool in general populations and in patients with ESRD [11,12,18,19]. SF-12, a shortened version of the SF-36 questionnaire has recently been introduced, but it has been rarely used for patients on dialysis, despite the advantage that it comprises only one third of the items compared to SF-36 [20]. The SF-12 was recently employed in a U.S. study on a large cohort of 44 395 patients on dialysis. Those authors concluded that the physical (PCS) and mental composite summary (MCS) scores based on the SF-12 were valid in this patient group. Furthermore, they showed that the prognostic information with regard to mortality was similar to that of the SF-36 [21]. To the best of our knowledge, the SF-12 has not been specifically validated in Europe for patients on dialysis; nor has any European study examined whether the SF-12-based HRQOL scores might be predictive of mortality. As the self-perceived HRQOL has been shown to diverge between countries, it is important to undertake studies of HRQOL in different countries. We suggest that the component summary scores from SF-12 and SF-36 are highly correlated. Furthermore, we hypothesized that self-assessed HRQOL based on the SF-12 and the SF-36 would provide similar predictions of mortality in patients on dialysis.

The objectives of the present study were to assess HRQOL with SF-12 and SF-36 and compare their abilities to predict mortality in chronic dialysis patients, after adjusting for traditional risk factors.

Methods

Study patients and design

In this observational prospective cohort study, the primary aim was to determine the association between HRQOL and mortality. We included a total of 301 prevalent dialysis patients (243 on hemodialysis and 58 on peritoneal dialysis) from ten dialysis clinics in Norway. Baseline HRQOL data were previously reported [22]. All adult patients (≥18 years old) that had received hemodialysis (HD) or peritoneal dialysis (PD) for more than 2 months were screened for study participation. Patients were excluded from the study when they were hospitalized during the investigation period; however, they could be enrolled four weeks or more after hospital discharge, if they were in stable clinical condition. Patients were excluded that displayed severely impaired cognitive function, psychosis, or drug abuse. The study required adequate Norwegian language skills. Signed informed consent was required for enrollment, after patients received oral and written information about the study. Detailed information regarding mortality and cause of death was obtained from the Norwegian Renal Registry. Patients were enrolled in the study from August 2005 to February 2007, and they were followed until January 2010. The recruitment process was described in detail previously [22]. Briefly, of the 416 patients considered eligible for the study, 326 patients consented to study participation, and 301 could be enrolled (enrollment rate of 72.4%). Patients with observation time less than 2 months were excluded from the survival analyses (Figure 1), and the time of renal transplantation was censored. To ensure standardized conditions, self-administered questionnaires were completed during the regular hemodialysis sessions for patients on HD or during the scheduled visit at the outpatient clinic for patients on PD. Study nurses and physicians were specifically trained in applying the study instruments.

The National and Regional Committees for Research Ethics in Norway approved the study protocol, and permission was obtained from the National Data Inspectorate.

Demographic and clinical data at baseline

Demographic data including age, gender, and work status were collected from reviews of hospital charts and/or by directly questioning the patients. The cause of renal failure, dialysis modality, dialysis vintage, comorbidities, and laboratory data were gathered from medical records. Comorbidity was measured with the modified Charlson comorbidity index (CCI) [23]. The CCI is a composite score of 17 multiple comorbid conditions (e.g., coronary artery disease and congestive heart failure) and age. In this study, CCI was

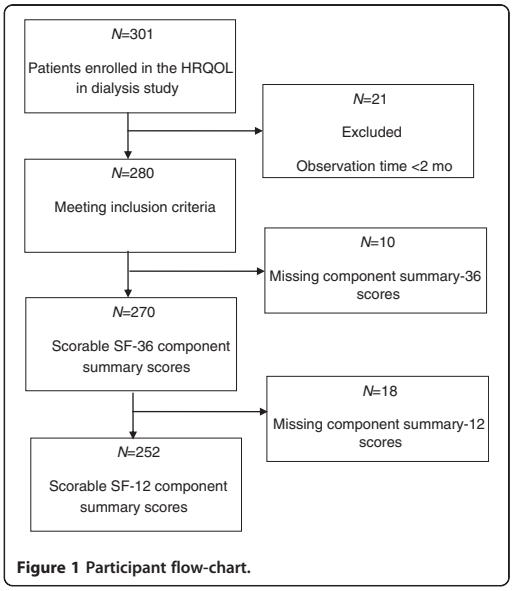

Figure 1 Participant flow-chart.

Table 1 Demographic and clinical baseline data for the study patients (n = 252), according to physical and mental component summary-36 score quartiles

	All patients	Physical component summary-36 score quartiles					Mental component summary-36 score quartiles				
		Q_1 Range: 9.6-30.0	Q_2 Range: 30.1-35.6	Q_3 Range: 35.7-44.4	Q_4 Range: 44.5–58.2	P -value	Q_1 Range: 16.9-39.2	Q_2 Range: 39.3-49.0	Q_3 Range: 49.1-55.6	Q_4 Range: 55.7-70.7	P - value
N	252	63	63	63	63		63	63	63	63	
Age, yrs, (252)	60.2±15.5	60.8±12.4	64.8±14.9	58.1±17.3	57.2±16.0	0.027[p]	56.5±15.7	63.7±15.3	60.0±17.0	60.6±13.0	0.071[p]
Male gender,%, (n=252)	65.9 (166)	58.7 (37)	68.3 (43)	69.8 (44)	66.7 (42)	0.563[2]	61.9 (39)	68.3 (43)	77.8 (49)	55.6 (35)	0.056[2]
Current smoker, %, (n=252)	25.8 (65)	33.3 (21)	23.8 (15)	22.2 (14)	23.8 (15)	0.466 [2]	39.7 (25)	22.2 (14)	19.0 (12)	22.2 (14)	0.034[2]
Work status, %, (n)											
Able to work, (n=235)	12.3 (29)	8.5 (5)	5.2 (3)	12.1 (7)	23.3 (14)	0.016 [2]	6.7 (4)	15.3 (9)	12.7 (7)	14.8 (9)	0.460[2]
Disable to work, (n=235)	51.5 (121)	64.4 (38)	43.1 (25)	50.0 (29)	48.3 (29)	0.118 [2]	65.0 (39)	35.6 (21)	47.3 (26)	57.4 (35)	0.009[2]
Retired, (n=235)	36.2 (85)	27.1 (16)	51.7 (30)	37.9 (22)	28.3 (17)	0.02 [2]	28.3 (17)	49.2 (29)	40.0 (22)	27.9 (17)	0.045[2]
Cause of renal failure, %, (n)											
Glomerulonephritis, (n=249)	20.5 (51)	14.3 (9)	20.6 (13)	19.4 (12)	27.9 (17)	0.311 [2]	20.6 (13)	12.7 (8)	26.7 (16)	22.2 (14)	0.276[2]
Diabetic nephropathy, (n=249)	14.1 (35)	22.2 (14)	6.3 (4)	16.1 (10)	11.5 (7)	0.068 [2]	15.9 (10)	14.3 (9)	16.7 (10)	9.5 (6)	0.663[2]
Hypertensive kidney disease, (n=249)	24.9 (62)	25.4 (16)	25.4 (16)	27.4 (17)	21.3 (13)	0.886 [2]	25.4 (16)	25.4 (16)	23.3 (14)	25.4 (16)	0.991[2]
Other, (n=249)	40.6 (101)	38.1 (24)	47.6 (30)	37.1 (23)	39.3 (24)	0.613 [2]	38.1 (24)	47.6 (30)	33.3 (20)	42.9 (27)	0.408[2]
Clinical variables											
Dialysis vintage, mo, (n=251)	9.0 (5.0, 23.0)	18.0 (6.0, 34.0)	9.0 (4.0, 20.0)	9.0 (5.0, 20.0)	7.0 (3.4, 16.8)	0.004[np]	10.0 (4.0, 23.0)	11.0 (5.0, 32.0)	10.0 (5.0, 17.3)	7.0 (4.0, 24.0)	0.352[np]
Previous graft failure, (251)	18.7 (47)	24.2 (15)	11.1 (7)	19.0 (12)	20.6 (13)	0.287 [2]	22.2 (14)	17.5 (11)	21.0 (13)	14.3 (9)	0.661[2]
Accepted for renal transplantation, (n=252)	38.1 (96)	28.6 (18)	27.0 (17)	49.2 (31)	47.6 (30)	0.01[2]	36.5 (23)	33.3 (21)	42.9 (27)	39.7 (25)	0.718[2]
Peritoneal dialysis, (n=252)	20.2 (51)	23.8 (15)	14.3 (9)	27.0 (17)	15.9 (10)	0.221 [2]	14.3 (9)	19.0 (12)	31.7 (20)	15.9 (10)	0.062[2]
Body mass index, kg/m^2, (n=235)	24.9±4.9	23.6±5.0	25.5±4.8	24.9±4.6	25.5±5.0	0.135[p]	23.7±4.5	25.2±4.4	25.0±4.6	25.9±5.8	0.124[p]
Serum albumin, g/l, (n=246)	38.0±4.8	36.6±5.9	37.7±4.4	38.4±4.3	39.1±4.0	0.022[p]	38.7±3.9	37.8±4.4	38.1±5.5	37.4±5.2	0.503[p]
Hemoglobin, g/dl, (n=246)	12.1±1.5	12.0±1.4	12.1±1.5	12.2±1.5	12.2±1.4	0.87[p]	11.8±1.6	12.1±1.3	12.4±1.5	12.2±1.3	0.139[p]
Total cholesterol, mmol/L, (n=230)	4.2±1.1	4.0±1.2	4.1±1.1	4.5±1.1	4.2±1.1	0.103[p]	4.3±1.2	4.0±1.0	4.2±1.2	4.3±1.1	0.279[p]
Comorbidity											
Diabetes, %, (n=250)	26.4 (66)	31.7 (20)	28.6 (18)	24.2 (15)	21.0 (13)	0.537 [2]	30.2 (19)	33.3 (21)	27.9 (17)	14.3 (9)	0.077[2]
CCI without age, (n=248)	4 (2, 5)	5 (4, 6)	4 (2, 4)	3 (2, 5)	3 (2, 4)	<0.001[np]	4 (3, 5)	4 (3, 5)	4 (2, 5)	3 (2, 5)	0.436[np]

CCI Charlson modified comorbidity index. Continuous variables are given as mean ± SD, when normally distributed, or as median (IQR), when skewed. P-values between the four groups are calculated based on parametric (ANOVA)[p] , nonparametric (Kruskall Wallis)[np], or Chi-squared[2] statistics. Note: Numbers of complete data are given in parentheses for each variable.

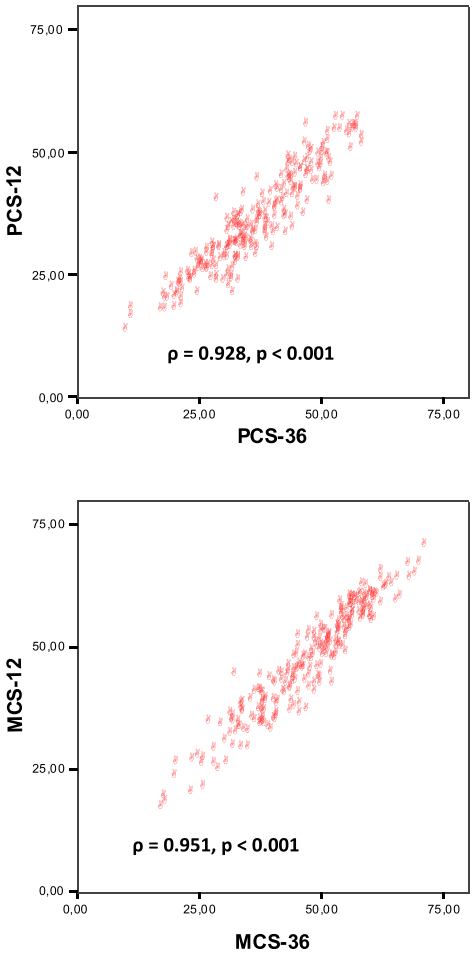

Figure 2 Scatter plots display correlations between physical and mental component summary scores (PCS and MCS, respectively). The scores were calculated from the SF-12 (ordinate) and SF-36 (abscissa) assessments of health related quality of life in patients on chronic dialysis (n = 252).

calculated without age, because we intended to evaluate the effect of age as a separate factor in the multivariate analysis.

Assessment of HRQOL

The Medical Outcome Study 36-item Short-Form health survey (SF-36) [18] was applied to assess the general dimensions of HRQOL. A validated Norwegian version of the SF-36 version 1 was applied [24]. The physical component summary (PCS-36) and the mental component summary (MCS-36) scores were derived from eight SF-36 subscales, as described by Ware et al. [25]. These scores ranged from 0 to 100, where a higher score represented better self-assessed health. The embedded SF-12 comprises 12 questions from the SF-36, and the component summary scores of SF-12 were calculated with the algorithm from the KDQoL working group (http://gim.med.ucla.edu/kdqol/downloads). The PCS-36 and PCS-12 included physical functioning, physical role limitation, and bodily pain; the MCS-36 and MCS-12 included mental health, social functioning, and emotional role limitation. General health and vitality were incorporated in all component summary scores. Recent reports showed strong correlations between the PCS-36 and PCS-12 and between MCS-12 and MCS-36 in patients with ESRD [21].

Statistical analyses

Clinical, demographic, and HRQOL variables were expressed as means and standard deviations (SDs), or medians with interquartile ranges (IQR), when data were skewed. Categorical variables were measured as frequencies and percentages. The one-way analysis of variance (ANOVA) or Kruskall-Wallis tests for skewed data were used to compare continuous variables between more than two groups; the Student's *t*-test or the Mann–Whitney test for skewed data was applied for comparisons between two groups. The chi-square test was used to compare categorical variables. HRQOL component summary scores (PCS-36, MCS-36, PCS-12 and MCS-12) were divided into quartiles, with equal number of patients in each quartile group (n = 63). Although HRQOL is considered a continuous variable, we implemented quartiles to reveal clinically significant differences. Kaplan-Meier curves were applied to compare survival rates between groups with different HRQOL quartile scores. Cox proportional hazard models were used to estimate the unadjusted and adjusted hazard ratios (HRs) of death for groups with different HRQOL quartile scores, and for changes in continuous HRQOL scales by one-unit increments. HRs are presented with 95% confidence intervals. In quartile analyses, the upper quartile (best perceived state) was used as the reference level. All demographic and clinical variables listed in Table 1 were set as independent variables in separate univariate Cox regression analyses to identify variables significantly associated with death; variables with $p < 0.2$ were entered into the adjusted Cox regression model as covariates. Spearman's correlations were performed to determine associations between the demographic and clinical variables and HRQOL component summary scores (PCS-36 and MCS-36). When a variable was significantly associated ($p < 0.2$) with both death and the PCS-36 or MCS-36 score, it was considered a potential confounder. When the Spearman's correlation coefficient between two potential confounders was outside the interval –0.70, 0.70, one was excluded.

Table 2 Impact of demographic and clinical variables on mortality in chronic dialysis patients (n = 252) during follow-up (median follow-up time 3.6 years), univariate associations are shown

	Hazard ratio	95% CI	p-value
Age, per year increment	1.026	1.009 – 1.044	0.002
Gender, male vs female	1.209	0.768 – 1.901	0.412
Currents smoking, yes vs no	1.772	1.125 – 2.790	0.014
Work status			
Able to work, yes vs no	0.510	0.186 – 1.398	0.191
Disable to work, yes vs no	1.030	0.659 – 1.610	0.896
Retired, yes vs no	1.162	0.743 – 1.819	0.510
Cause of renal failure			
Glomerulonephritis, yes vs no	1.015	0.571 – 1.804	0.959
Diabetic nephropathy, yes vs no	1.704	0.987 – 2.942	0.056
Hypertensive kidney disease, yes vs no	1.147	0.723 – 1.821	0.560
Clinical variables			
Dialysis vintage, per month increment	1.009	0.998 – 1-020	0.095
Log-dialysis* vintage, per unit increment	1.284	1.041 – 1.585	0.020
Previous graft failure, yes vs no	1.748	0.926 – 3.299	0.085
Rejected for renal transplantation, yes vs no	1.965	1.063 – 3.635	0.031
Dialysis modality, hemodialysis vs. peritoneal dialysis	1.091	0.632 – 1.883	0.755
Body mass index, per unit (kg/m^2) increment	0.985	0.939 – 1.034	0.536
Albumin, per unit (g/l) increment	0.978	0.937 – 1.012	0.176
Hemoglobin, per unit (g/dl) increment	0.879	0.758 – 1.019	0.088
Cholesterol, per unit (mmol/l) increment	0.937	0.747 – 1.176	0.574
Diabetes, yes vs no	1.579	1.002 – 2.487	0.049
Charlsons modified comorbidity index without age, per unit increment	1.260	1.136 – 1.398	<0.001

*Log-transformed dialysis vintage.
Abbreviations: *CI* confidence interval.

To identify the most important covariates, all selected variables were entered into multivariate linear regression models with PCS-36 and MCS-36 as dependent variables. By backward variable selection, only variables with $p < 0.1$ were analyzed further.

Age, dialysis vintage, and the Charlson comorbidity index were included in the final model as covariates. Due to the selection criteria, serum albumin was included in the model that examined the relationship between death and the PCS-36 or PCS-12 quartile score. Hemoglobin was included in the model that examined the relationship between death and the MCS-36 or MCS-12 quartile score. Gender was included as a covariate in the final model, despite the lack of significant associations with death. When a variable markedly deviated from a normal distribution, data were log-transformed (e.g., dialysis vintage) before inclusion into the regression model as a covariate [26].

The significance level was set to 5%. The data were analyzed with SPSS for Windows, version 16 (SPSS, Chicago, IL, USA).

Results

Of the 301 patients enrolled in the study, 21 patients were excluded from the survival analysis due to short observation time (< 2 months). Ten patient SF-36 component summary scores were missing, and additionally 18 patient SF-12 component summary scores. Thus, data from 252 patients was analyzed (Figure 1). The follow-up time ranged from 2.8 to 4.5 years, with a median of 3.6 years (IQR 3.2 to 3.9). The time from study inclusion to death or kidney transplantation ranged from 0.2 to 4.3 years, with a median time of 1.5 years (IQR 0.9 to2.7). At the end of follow-up, 85 (33.7%) patients had died, and 122 (48.4%) patients had received a renal transplant.

Highly significant correlations were observed between the PCS-36 and PCS-12 ($r = 0.932$, $\rho = 0.928$, $p < 0.001$ for both, $n = 252$, Figure 2), and between the MCS-36 and MCS-12 ($r = 0.953$, $\rho = 0.951$, $p < 0.001$ for both, $n = 252$, Figure 2).

Characteristics of the patients, grouped by quartiles of PCS-36 and MCS-36, are presented in Table 1. For the

whole study population (n = 252), the mean scores for PCS-36 was 36.6 ±10.4 (range 9.6 - 58.2), the MCS-36 was 47.3 ±11.0 (16.9 -70.7), PCS-12 was 35.5 ± 9.9 (13.3 – 56.6), and MCS-12 was 46.9 ± 10.9 (16.7 -70.4). Age, dialysis vintage, serum albumin, and comorbidity differed between PCS-36 quartiles; age, smoking, and workability differed between MCS-36 quartiles (Table 1).

The most frequent causes of death were cardiovascular disease 42.4% (n = 36), sepsis 31.8% (n = 27), and malignant disease 14.1% (n = 12). Withdrawal from dialysis occurred in 4.7% (n = 4). In univariate Cox regression analyses (Table 2), mortality was significantly associated with age, current smoking, log transformed dialysis vintage, being rejected for renal transplantation, presence of diabetes and comorbidity score. In contrast, mortality was not associated with gender, dialysis modality, hemoglobin, previous graft failure, serum albumin, body mass index, or cholesterol.

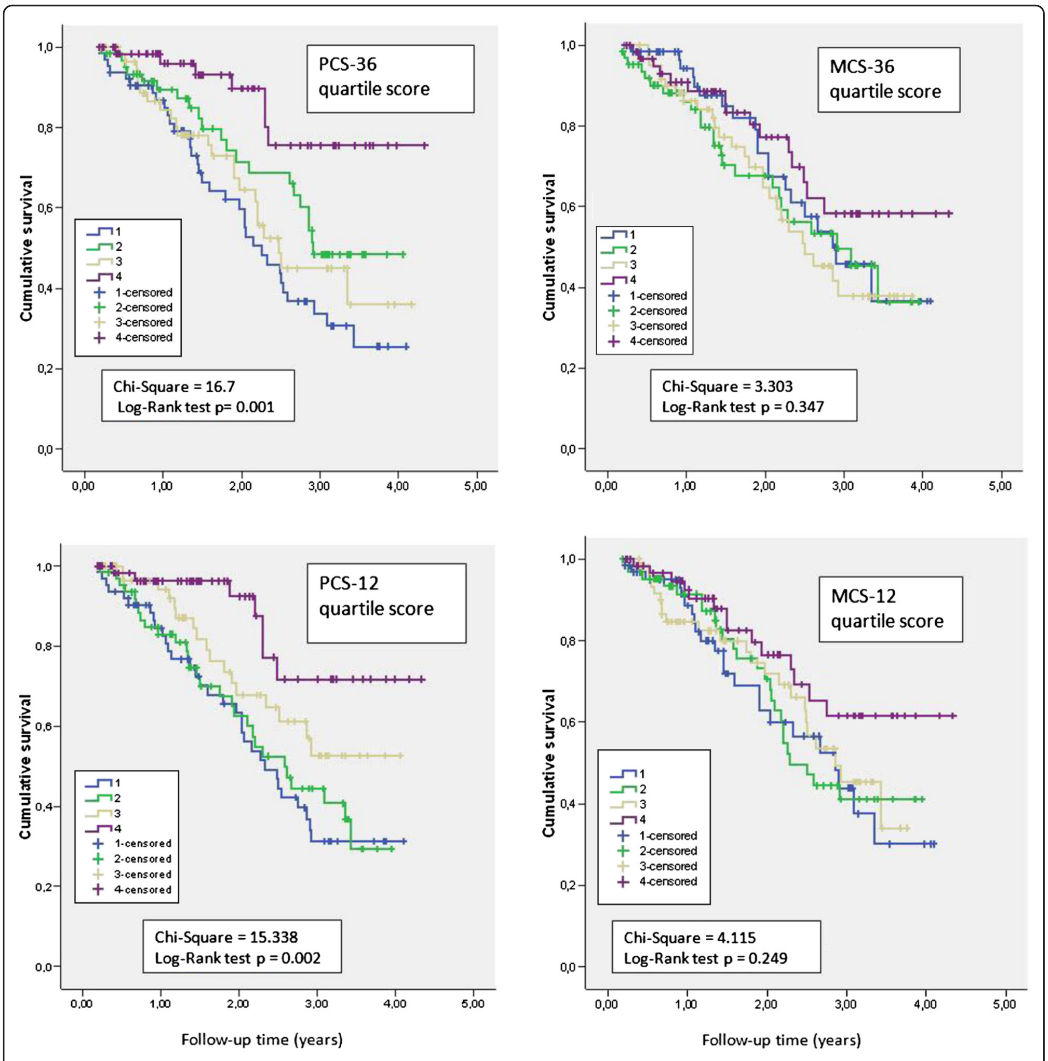

Figure 3 Kaplan-Meier plots of mortality rates in quartiles (Q1-Q4) of physical (left, PCS) and mental (right, MCS) component summary scores. Scores were calculated with the SF-36 (n = 252, upper panels) or SF-12 (n = 252, lower panels) assessments in patients on chronic dialysis.

Mortality rates were significantly different in the highest and lowest PCS-12 quartiles, based on the Kaplan Meier curves (Figure 3). A similar difference was observed for PCS-36 quartiles (Figure 3). In contrast, mortality rates were not different between quartiles for either the MCS-36 or MCS-12 (Figure 3, Table 3).

The unadjusted and multi-adjusted hazard ratios of death were assessed for SF-12 and SF-36 quartile scores (Table 3). After multiple adjustment, for the PCS-12, patients with the lowest quartile score had a 2.5-fold higher risk of death compared to patients in the highest quartile i.e., the best perceived state. For the PCS-36 quartiles, the corresponding difference in risk was 2.7 after multiple adjustments.

The unadjusted and multi-adjusted HRs of death were also assessed for continuous SF-12 or SF-36 component summary scores (Table 4). During the follow-up, a one-unit increase in the PCS-12 score was related to 3.2% lower adjusted HR of death; a one-unit increase in the PCS-36 score was related to 2.3% lower adjusted HR of death.

Discussion

We found that poor self-assessed physical health was an independent predictor of mortality in Norwegian patients on dialysis, after adjusting for established risk factors. This was consistent with results previously shown in other populations [11-14]. Beyond the confirmatory observation that low self-perceived physical aspect of HRQOL score is associated with higher risk of death, our results expand that finding that SF-12, as well as SF-36 revealed the increased mortality risk. In our study, one unit increase in PCS-12 score predicted 3.2% decreased adjusted HR of death, and one unit of increase in PCS-36 score 2.3% decreased adjusted HR of death. The great advantage of using SF-12 is that it comprises fewer items, it is less time-consuming, and easier to use, and thus, may represent a more clinically applicable tool for monitoring HRQOL. The latter observation was in accordance with the recent US study reporting that each incremental PCS-12 and PCS-36 point was associated with a 2.4% lower adjusted HR of death during a one year follow-up [21]. In our study, the adjusted HR of death was tripled, in patients in the lowest PCS-12 quartile compared to those in the highest quartile over the three to four-year period. The findings support the concept that a poor self-assessed HRQOL is an important risk factor for death, and it should not be ignored. Thus, measurement of HRQOL should be included in the general clinical work-up and follow-ups of patients on dialysis.

In contrast to some [12,13,15], but not all [11,16] other studies, we did not find any significant association between self-assessed mental health and mortality. Although we observed 1.1% reduction in the hazard ratio of death for every one-unit increase in MCS-12, this was not statistically significant. However, the magnitude was consistent with the 1.2% reduction in the adjusted hazard ratio of death recently reported by a large US study on patients on chronic dialysis [21]. The sample size in our study was most likely too small to reveal a significant relationship between death and MCS. Conflicting results have been reported in the literature on the effect of mental health on mortality. Nevertheless, the mental health effect has consistently been less than the effect of self-perceived physical health. Although the level of self-perceived mental health in the general population may differ among countries, the MCS scores in the large US study population [21] were similar to the MCS in our study population, and they observed that MCS as well as PCS predicted mortality. In this study, we excluded patients with cognitive disturbance, psychosis or drug-abuse. This exclusion may have affected the level of self-perceived mental health in our population, and could have led to a lower likelihood of predicting mortality. In at least some studies, a poor MCS score has been related to higher levels of depression, and depression has been shown to predict mortality in patients on chronic dialysis [27,28].

Table 3 Unadjusted and multi-adjusted hazard ratios (HRs) for mortality were assessed for patients on dialysis, grouped by physical and mental component summary (PCS-36, MCS-36, PCS-12, and MCS-12) quartile scores

	PCS-36 quartile score				MCS-36 quartile score			
	Unadjusted HR(95% CI)	p-value	Adjusted[A] HR (95% CI)	p-value	Unadjusted HR(95% CI)	p-value	Adjusted[B] HR(95% CI)	p-value
Q^4	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q^3	3.516(1.508, 8.196)	0.004	2.495(1.041, 5.976)	0.040	1.720(0.911, 3.249)	0.095	1.262(0.616, 2.584)	0.525
Q^2	2.599(1.104, 6.119)	0.029	1.741(0.721, 4.205)	0.218	1.634(0.857, 3.115)	0.136	1.460(0.735, 2.898)	0.280
Q^1	4.547(2.016, 10.259)	<0.001	2.675(1.126, 6.355)	0.026	1.365(0.698, 2.667)	0.363	1.676(0.845, 3.327)	0.714
	PCS-12 quartile score				MCS-12 quartile score			
Q^4	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q^3	2.248(0.932, 5.423)	0.072	1.658(0.630, 4.365)	0.306	1.262(0.616, 2.584)	0.525	1.671(0.859, 3.250)	0.130
Q^2	3.618(1.584, 8.263)	0.002	2.423(0.964, 6.087)	0.060	1.460(0.735, 2.898)	0.280	1.746(0.907, 3.61)	0.095
Q^1	4.056(1.789, 9.194)	0.001	2.512(1.009, 6.254)	0.048	1.676(0.845, 3.327)	0.140	1.901(0.978, 3.368)	0.058

Table 4 Unadjusted and multi-adjusted hazard ratios (HRs) for mortality were assessed for patients on dialysis (n = 252) grouped by continuous physical and mental component scores (PCS-36, MCS-36, PCS-12, and MCS-12), based on the SF-36 and SF-12

	Unadjusted HR(95% CI)	p-value	Adjusted HR(95% CI)	p-value
PCS-36 (per one increment unit)	0.963(0.943, 0.984)	0.001	0.977(0.953, 1.002)	0.077
PCS-12 (per one increment unit)	0.954(0.931, 0.977)	<0.001	0.968(0.942, 0.995)	0.022
MCS-36 (per one increment unit)	0.989(0.970, 1.008)	0.248	0.995(0.976, 1.015)	0.649
MCS-12 (per one increment unit)	0.981(0.961, 1.001)	0.057	0.989(0.968, 1.011)	0.339

The PCS-36 and PCS-12 were adjusted for age, gender, Charlsons comorbidity index without age, log transformed dialysis vintage, and albumin. The MCS-36 and MCS-12 are adjusted for age, gender, Charlsons comorbidity index without age, log transformed dialysis vintage, and hemoglobin.

As suggested by Ware et al. [29], the use of SF-12, either interspersed within the SF-36, or on its own, has shown excellent correlations to the SF-36. The strong correlations that we observed between the SF-12 and SF-36 summary scores were consistent with findings in the general Norwegian population [30]. A recent cross-validation of the selected items for SF-12 was conducted in nine European countries; this led to the conclusion that data from the SF-12 were comparable to standard benchmarks [30]. Thus, our data extend that finding to include patients on chronic dialysis.

Some clinical and demographic characteristics of our study population were notable. The prevalence of diabetes in our study population was 26%, which is lower than that reported in other HRQOL studies; e.g., 66% was reported in the Spanish CALVIDA study [15], and nearly 50% was reported in a recent US study [21]. Diabetes has been a less prevalent cause of renal disease in Norwegian patients with ESRD compared to US patients on chronic dialysis [31]. Furthermore, in our study, the patients had undergone regular dialysis over a shorter period than that reported in other studies [15,21]. This was due to the high renal transplantation rate in Norway [32,33].

Strengths and limitations of the study

One of the strengths of this study was that the sample was fairly large; it comprised close to one-third of the total population on regular dialysis in Norway at the time of sample selection [34]. In addition, the participation rate in the health survey was high, and none was lost to follow-up. The multi-center design ensured inclusion of patients from both rural and urban areas. Furthermore, socioeconomic status did not affect the possibility of dialysis. The characteristics of our patient population were quite similar to those of the general Norwegian population of patients on dialysis [34] in age, gender, and cause of renal failure. However, a selection bias could not be excluded, because the healthiest patients, both physically and mentally, might be more likely to participate in the study. Our data may underestimate the effect of HRQOL on clinical outcome, as patients with psychosis, drug abuse, cognitive disturbances, or recent hospitalization due to serious medical conditions were excluded. In this study we were committed to use the SF-36 version 1, in order to compare our results with Norwegian reference population [22,24]. Complete component summary scores could not be calculated for 10 patients in the SF-36 and for an additional 18 in the SF-12, due to missing single items. Only seven of the 301 patients were non-Caucasians; thus, the results may not be applicable to other populations. Furthermore, the renal transplantation rate in Norway is among the highest in Europe [32,35]. This affected the total time spent on chronic dialysis. During follow-up, 47% of patients received a kidney transplant in this study.

Conclusions

Self-assessed physical health based on either the PCS-12 or PCS-36 is a strong, independent predictor of mortality in patients on chronic dialysis. The PCS-12 and PCS-36 provided comparable results. Thus, the physical aspects of HRQOL may increase the accuracy of risk stratification by adding important prognostic information for patients on dialysis. We suggest that the HRQOL assessment should be included in clinical investigations. Because the SF-12 requires less time to complete than the SF-36, it should be used routinely to assess HRQOL, in addition to the traditional, risk factors. It remains to be determined whether specific interventions aimed to improve HRQOL would affect the composite scores of either SF-12 or SF-36 and translate to improved survival.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

IO, TD, IHN and LS prepared the study protocol and designed the study. TBHØ and VTP collected the data. TL provided data from the Norwegian Renal Registry on mortality and transplantation. TBHØ drafted the manuscript. TBHØ conducted the statistical analyses supervised by LS. TBHØ and IO interpreted the results. All co-authors critically reviewed the manuscript for important intellectual content and approved the final version to be published.

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Appendix

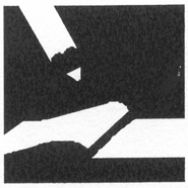
Din helse

– og –

ditt velbefinnende

Kidney Disease and Quality of Life (KDQOL-SF™ 1.3)

Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.



Takk for at du svarer på disse spørsmålene!

Oversatt til norsk 2005 av Ingrid Os, overlege, professor, Nyremedisinsk avdeling, Tone Brit Hortemo Østhus, lege, stipendiat, Nyremedisinsk avdeling, Toril Dammen, overlege 1. amanuensis, Psykiatrisk avdeling , Ullevål universitetsykehus,og Fakultetsdivisjon på Ullevål, Universitetet i Oslo, Inger Hilde Nordhus, professor, Psykologisk institutt, Universitetet i Bergen . Spørsmål 1-11 bygger på norsk oversettelse av SF36 ved Jon Håvard Loge , professor , Kompetansesenter for lindrende behandling, Kirugisk divisjon , Ullevål universitetssykehus og Kjell Kaasa, assisterende seksjonsleder, Prehospital Divisjon Aurskog/Høland ambulanse

1. Stort sett, vil du si at din helse er:

- ☐ Utmerket
- ☐ Meget god
- ☐ God
- ☐ Nokså god
- ☐ Dårlig

2. <u>Sammenlignet med for ett år siden,</u> hvordan vil du si at din helse stort sett er nå?

- ☐ Mye bedre nå enn for ett år siden
- ☐ Litt bedre nå enn for ett år siden
- ☐ Omtrent den samme som for ett år siden
- ☐ Litt dårligere enn for ett år siden
- ☐ Mye dårligere enn for ett år siden

3. De neste spørsmålene handler om aktiviteter du kanskje utfører i løpet av en vanlig dag.
Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene nå? Hvis ja, hvor mye?

AKTIVITETER	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
a. Anstrengende aktiviteter som å løpe, løfte tunge gjenstander delta i anstrengende idrett	☐	☐	☐
b. Moderat aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid	☐	☐	☐
c. Løfte eller bære en handlekurv	☐	☐	☐
d. Gå opp trappen flere etasjer	☐	☐	☐
e. Gå opp trappen en etasje	☐	☐	☐
f. Bøye deg eller sitte på huk	☐	☐	☐
g. Gå mer enn to kilometer	☐	☐	☐
h. Gå noen hundre meter	☐	☐	☐
i. Gå hundre meter	☐	☐	☐
j. Vaske eller kle på deg	☐	☐	☐

4. I løpet av de siste 4 ukene, har du hatt noen av følgende symptomer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

	Ja	Nei
a. Du har måttet **redusere tiden** du har brukt på arbeid eller andre gjøremål	☐	☐
b. Du har **utrettet mindre** enn du har hadde ønsket	☐	☐
c. Du har **vært** hindret i å utføre **visse typer** arbeid eller gjøremål	☐	☐
d. Du har hatt **problemer** med å gjennomføre arbeid eller andre gjøremål (f.eks. fordi det krevde ekstraanstrengelser)	☐	☐

5. I løpet av de siste 4 ukene, har du hatt noen av følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din følelsesmessige problmer (som f.eks å være deprimert eller engstelig)**?**

	Ja	Nei
a. Du har måttet **redusere tiden** du har brukt på arbeid eller andre gjøremål	☐	☐
b. Du har **utrettet mindre** enn du har hadde ønsket	☐	☐
c. Du har utført arbeid eller andre gjøremål **mindre grundig** enn vanlig	☐	☐

6. I løpet av de siste 4 ukene, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?

☐ Ikke i det hele tatt ☐ Litt ☐ En del ☐ Mye ☐ Svært mye

7. Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 ukene?

☐ Ingen ☐ Meget svake ☐ Svake ☐ Moderate ☐ Sterke ☐ Megest sterke

8. I løpet av de siste 4 ukene, hvor mye har smerte påvirket ditt daglige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?

☐ Ikke i det hele tatt ☐ Litt ☐ En del ☐ Mye ☐ Svært mye

9.De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de siste fire ukene. For hvert spørsmål vennligst velg det svaralternativ som best beskriver hvordan du har hatt det. Hvor ofte i løpet av de siste fire ukene har du:.

	Hele tiden	Neste hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
a. følt deg full av tiltakslyst	☐	☐	☐	☐	☐	☐
b. følt deg veldig nervøs	☐	☐	☐	☐	☐	☐
c. Vært så langt nede at ingenting kunne muntre deg opp	☐	☐	☐	☐	☐	☐
d. Følt deg rolig og harmonisk	☐	☐	☐	☐	☐	☐
e. Hatt mye overskudd	☐	☐	☐	☐	☐	☐
f. Følt deg nedfor og trist	☐	☐	☐	☐	☐	☐
g. Følt deg sliten	☐	☐	☐	☐	☐	☐
h. Følt deg glad	☐	☐	☐	☐	☐	☐
i. Følt deg trett	☐	☐	☐	☐	☐	☐

10. I løpet av de siste 4 ukene, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som å besøke venner, slektninger osv.)?

☐ Hele tiden ☐ Nesten hele tiden ☐ En del av tiden ☐ Litt av tiden ☐ Ikke i det hele tatt

11. Hvor RIKTIG eller GALT er hver av de følgende påstandene for deg?

	Helt riktig	Delvis riktig	Vet ikke	Delvis galt	Helt galt
a. Det virker som jeg blir syk litt lettere enn andre	☐	☐	☐	☐	☐
b. Jeg er like frisk som de fleste jeg kjenner	☐	☐	☐	☐	☐
c.Jeg tror at helsen min vil forverres	☐	☐	☐	☐	☐
d. Jeg har utmerket helse	☐	☐	☐	☐	☐

Din nyresykdom

12. Hvor RIKTIG eller GALT er hver av de følgende påstandene for deg?

	Helt riktig	Delvis riktig	Vet ikke	Delvis galt	Helt galt
a. Min nyresykdom forstyrrer for mye i livet mitt	☐	☐	☐	☐	☐
b. Jeg bruker for mye av tiden min på nyresykdommen min	☐	☐	☐	☐	☐
c. Det er frustrerende å beskjeftige seg med nyresykdommen min	☐	☐	☐	☐	☐
d. Jeg føler meg som en belastning for min familie	☐	☐	☐	☐	☐

13. Disse spørsmålene handler om hvordan du har hatt det i løpet av de siste 4 uker. Hvert spørsmål besvares ved å krysse av for det alternativet som best beskriver hvordan du har hatt det.

(Sett ett kryss på hver linje)

	Ikke i det hele tatt	Litt av tiden	En del av tiden	Mye av tiden	Nesten hele tiden	Hele tiden
a. Har du isolert deg fra mennesker omkring deg	☐	☐	☐	☐	☐	☐
b. Har du reagert langsomt på ting, som har blitt sagt eller gjort	☐	☐	☐	☐	☐	☐
c. Har du vært irritert på de som har vært rundt deg?	☐	☐	☐	☐	☐	☐
d. Har du hatt vanskelig for å konsentrere deg eller for å tenke?	☐	☐	☐	☐	☐	☐
e. Har du kommet bra overens med andre mennesker?	☐	☐	☐	☐	☐	☐
f. Har du vært forvirret?	☐	☐	☐	☐	☐	☐

14. I løpet av de siste 4 uker, hvor mye har du vært plaget av følgende (Sett ⊗ én boks på hver linje)

	Ikke plaget i det hele tatt	Litt plaget	noe plaget	mye plaget	veldig mye plaget
a Ømme muskler	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
b Brystsmerter	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
c Kramper	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
d Hudkløe	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
e Tørr hud	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
f Kortpustethet	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
g Svimmelhet eller nesten besvimelse.	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
h Mangel på appetitt	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
i Utkjørt eller utbrendt	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
j Nummenhet i hender eller føtter	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
k Kvalme eller brekninger	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
(Besvares kun av hemodialyse pasienter)					
l Problemer med dialyseadgangen ? (fistel,kateter,graft)	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
(Besvares kun av peritoneal dialyse pasienter)					
m Problemer med kateterinngangen ?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

Din nyresykdoms påvirkning på ditt daglige liv

15. Noen personer er plaget av nyresykdommen i det daglige liv, mens andre ikke er det. Hvor mye plaget er du av din nyresykdom innen hvert av de følgende områder?
(Sett ⊗ én boks på hver linje)

	Ikke plaget i det hele tatt	Litt plaget	noe plaget	mye plaget	veldig mye plaget
a Begrensinger på hvor mye du kan drikke	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Kostrestriksjon	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Din evne til å klare arbeid i huset	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Din evne til å reise	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Din avhengighet av leger og annet helsepersonell	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Stress og bekymring forårsaket av din nyresykdom	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Ditt seksualliv	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Ditt utseende	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

De neste tre spørsmål er personlige og handler om din seksuelle aktivitet, men dine svar er viktige for å forstå hvordan nyresykdom påvirker menneskers liv.

16. Har du hatt noen form for seksuell aktivitet de siste 4 uker?
(sett en ring om ett tall)

Nei……1 ⇨ **Gå til spørsmål 17.**

Ja……..2

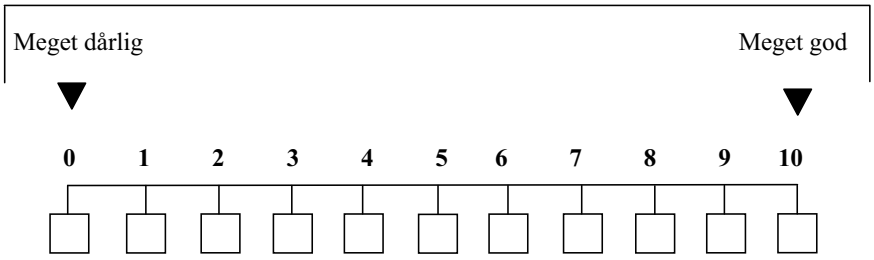
Hvor stort problem var følgende for deg i løpet av de siste 4 uker?
(Sett ⊗ i én boks på hver linje)

	Ikke problematisk	et lite problem	et moderat problem	et stort problem	et alvorlig problem
a Å nyte sex	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Å bli seksuelt opphisset	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

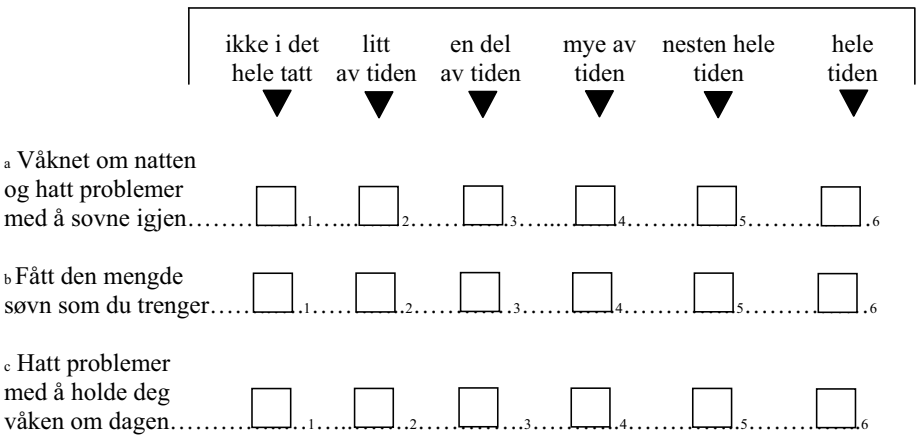
17. For å svare på det neste spørsmålet skal du bruke en skala fra 0 som betyr "svært dårlig" til 10 som er "svært bra"

Hvis du anser at din søvn er midt i mellom svært dårlig og svært bra, setter du et kryss ved nummer 5. Om du anser at søvnen er et trinn bedre enn 5, markerer du under 6. Om du anser at søvnen din er dårligere enn 5, markerer du under ruten 4 og så videre.

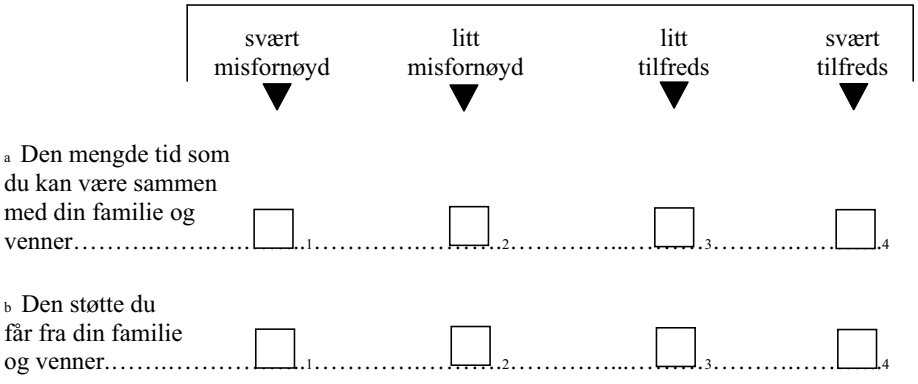
På en skala fra 0-10 hvordan vil du i det store og hele bedømme din søvn? (Sett ⊗ under ett tall)



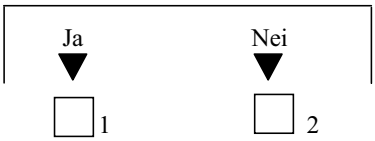
18. Hvor ofte de siste 4 uker har du…
(Sett ⊗ én boks på hver linje)



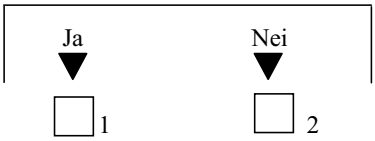
19. Vedrørende din familie og venner, hvor fornøyd er du med …
(Sett ⊗ i én boks på hver linje)



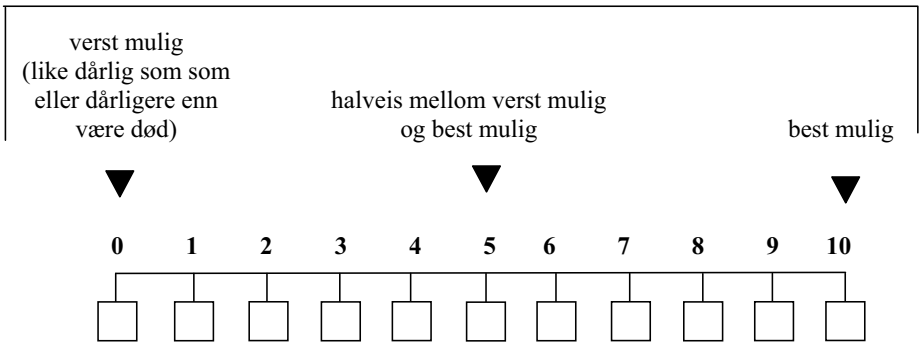
20. I løpet av de siste uker, har du hatt lønnet arbeid?



21. Har din helsetilstand hindret deg i å utføre lønnet arbeid?

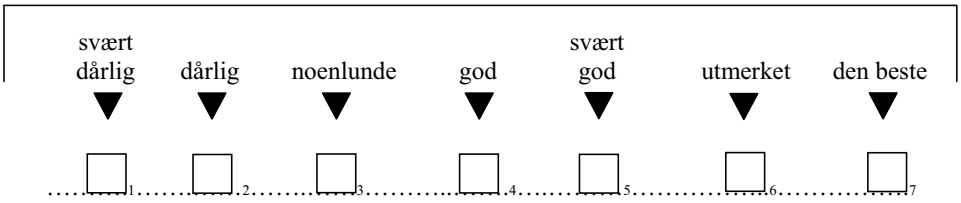


22. Totalt sett – hvordan vurderer du helsen din?
(Sett ⊗ under ett tall)

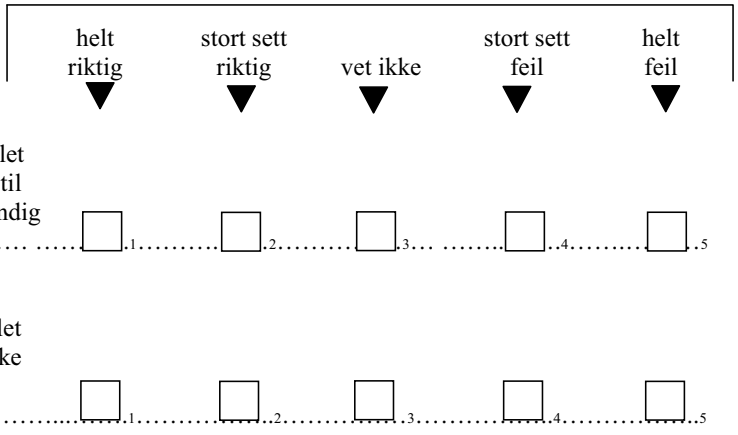


Tilfredshet med din behandling/omsorg

23. Tenk på den omsorg du mottar i forbindelse med dialysebehandling. Hvor tilfredsstillende vurderer du den vennlighet og den interesse som vises for din person?
(Sett ett ⊗)

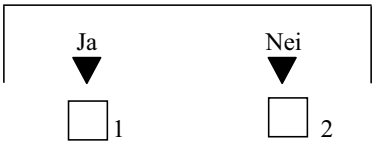


24. Velg det svaret som beskriver best hvordan hver og ett av de følgende påstandene er riktig eller galt for deg.
(Sett ⊗ i én boks på hver linje)



Bakgrunnsinformasjon

25. Tar du i øyeblikket noen reseptbelagte medisiner regelmessig (4 eller flere dager i uken) som er forordnet av legen for medisinsk behandling? Ikke ta med håndkjøpsmedisin som syrenøytraliserende medisiner eller hodepinetabletter



(hvis nei, gå videre til spørsmål 26)

25a. Hvor mange ulike reseptbelagte medisiner tar du nå?

Antall medisiner: _____

26. Hvor mage dager sammenlagt i løpet av de siste 6 måneder har du vært innlagt på sykehus (altså hvor du har overnattet på sykehus)?
Hvis svaret er ingen, skriv 0

Antall dager: _____

27. Hvor mange dager til sammen i løpet av de siste 6 mnd har du vært på sykehuset til behandling, men kommet hjem samme dag?
Hvis svaret er ingen, skriv 0

Antall dager: _____

28. Hva forårsaket din nyresykdom?

Sett ring rundt ett eller flere tall

Vet ikke…… 1
Høyt blodtrykk…… 2
Diabetes……... 3
Cystenyresykdom…… 4
Kronisk glomerulonefritt (nyrebetennelse)…… 5
Kronisk pyelonefritt (urinveisinfeksjoner)……. 6

Annet spesifiser_____ 7

29. Når er du født?

År/mnd/dag: _____/_____/_____

30. Hva er den høyeste avsluttete utdannelsen du har?
(Sett ring rundt ett tall)

Grunnskole eller ingen utdanning i det hele tatt…….…….1

Ungdomskole / realskole…….…2

Gymnas / yrkesskole ……...3

Universitet / høyskole utdanning……4

31. Har du i løpet av de siste 30 dager…
(Sett ring rundt et tall)

Arbeidet heltid…… 1

Arbeidet deltid……....2

Vært arbeidsløs, permittert eller arbeidsøkende…… 3

Mottatt alderspensjon…… 4

Mottatt uførepensjon…… 5

Studert…… 6

Vært hjemmeværende…….. 7

Ingen av de ovennevnte…… 8

32. Hva er din husholdnings totale inntekt (alle kilder) før skatt det siste kalenderåret inkludert deg selv, din ektefelle eller partner, og andre som du ser som familie, som er en del av din husholdning (svarene dine er konfidensielle)? (Sett ring rundt et tall)

Mindre enn 50 000 NOK……..... 1

50 001 – 100 000 NOK……...…… 2

100 001 – 200 000 NOK…..……..... 3

200 001 – 400 000 NOK…… 4

400 001 – 750 000 NOK…… 5

Mer enn 750 000 NOK…….. 6

Vet ikke…….. 7

33. Har noen hjulpet deg med å fylle ut dette spørsmålsskjemaet? (Sett ring rundt et tall)

Ja, en lege eller annet helsepersonell…… 1

Ja, et familiemedlem eller en venn……....2

Ja, noen annen…… 3

Nei…… 4

Vennligst skriv dagens dato: _____

Takk for at du deltok i undersøkelsen!

BECK INVENTORY

\beck-inv

Navn:_____ Alder:_____ Kjønn:_____

INSTRUKSJON: I dette spørreskjemaet vil du finne setninger inndelt i grupper. Vennligst les alle setningene innenfor hver gruppe nøye. Deretter velger du den setningen i hver gruppe som best beskriver hvordan du har følt deg **DEN SISTE UKA, I DAG INKLUDERT.** Sett så en ring rundt tallet utenfor setningen du har valgt. Dersom flere setninger innenfor samme gruppe synes å passe like godt, sett en ring rundt tallene til hver av dem.

Husk å lese alle setningene innenfor en gruppe før du velger, og pass på at du gir svar innenfor alle gruppene.

---

1. 0 Jeg føler meg ikke trist.
   1 Jeg er lei meg eller føler meg trist.
   2 Jeg er lei meg eller trist hele tiden og klarer ikke å komme ut av denne tilstand.
   3 Jeg er så trist eller ulykkelig at jeg ikke holder det ut.

2. 0 Jeg er ikke særlig pessimistisk eller motløs overfor fremtiden.
   1 Jeg føler meg motløs overfor fremtiden.
   2 Jeg føler at jeg ikke har noe å se frem til
   3 Jeg føler at fremtiden er håpløs og at forholdene ikke kan bedre seg.

3. 0 Jeg føler meg ikke som et mislykket menneske.
   1 Jeg føler at jeg har mislykkes mer enn andre mennesker.
   2 Når jeg ser tilbake på livet mitt, ser jeg ikke annet enn mislykkethet.
   3 Jeg føler at jeg har mislykkes fullstendig som menneske.

4. 0 Jeg får like mye tilfredsstillelse ut av ting som før.
   1 Jeg nyter ikke ting på samme måte som før.
   2 Jeg får ikke ordentlig tilfredsstillelse ut av noe lenger.
   3 Jeg er misfornøyd eller kjeder meg med alt.

5. 0 Jeg føler meg ikke særlig skyldbetynget.
   1 Jeg føler meg skyldbetynget en god del av tiden.
   2 Jeg føler meg temmelig skyldbetynget mesteparten av tiden.
   3 Jeg føler meg skyldbetynget hele tiden.

6. 0 Jeg har ikke følelsen av å bli straffet.
   1 Jeg føler at jeg kan bli straffet.
   2 Jeg forventer å bli straffet.
   3 Jeg føler at jeg blir straffet.

7. 0 Jeg føler meg ikke skuffet over meg selv.
   1 Jeg er skuffet over meg selv.
   2 Jeg avskyr meg selv.
   3 Jeg hater meg selv.

8. 0 Jeg føler ikke at jeg er noe dårligere enn andre.
   1 Jeg kritiserer meg selv for mine svakheter eller feilgrep.
   2 Jeg bebreider meg selv hele tiden for mine feil eller mangler.
   3 Jeg gir meg selv skylden for alt galt som skjer.

9. 0 Jeg har ikke tanker om å ta livet mitt.
   1 Jeg har tanker om å ta livet mitt, men jeg vil ikke omsette dem i handling.
   2 Jeg ønsker å ta livet mitt.
   3 Jeg ville ta livet mitt om jeg fikk sjansen til det.

10. 0 Jeg gråter ikke mer enn vanlig.
    1 Jeg gråter mer nå enn jeg gjorde før.
    2 Jeg gråter hele tiden nå.
    3 Jeg pleide å kunne gråte, men nå kan jeg ikke gråte selv om jeg gjerne vil.

11. 0 Jeg er ikke mer irritert nå enn ellers.
1 Jeg blir lettere ergerlig eller irritert enn før.
2 Jeg føler meg irritert hele tiden nå.
3 Jeg blir ikke irritert i det hele tatt over ting som pleide å irritere meg.

12. 0 Jeg har ikke mistet interessen for andre mennesker.
1 Jeg er mindre interessert i andre mennesker enn jeg pleide å være.
2 Jeg har mistet det meste av min interesse for andre mennesker.
3 Jeg har mistet all interesse for andre mennesker.

13. 0 Jeg tar avgjørelser omtrent like lett som jeg alltid har gjort.
1 Jeg forsøker å utsette det å ta avgjørelser mer enn tidligere.
2 Jeg har større vanskeligheter med å ta avgjørelser enn før.
3 Jeg klarer ikke å ta avgjørelser i det hele tatt lenger.

14. 0 Jeg føler ikke at jeg ser dårligere ut enn jeg pleide å gjøre.
1 Jeg er bekymret for at jeg ser gammel eller lite tiltrekkende ut.
2 Jeg føler at det er varige forandringer i mitt utseende som får meg til å se lite tiltrekkende ut.
3 Jeg tror at jeg ser stygg ut.

15. 0 Jeg kan arbeide omtrent like godt som før.
1 Det kreves en ekstra anstrengelse for å ta fatt på noe.
2 Jeg må presse meg selv meget hardt for å gjøre noe.
3 Jeg klarer ikke å gjøre noe arbeid i det hele tatt.

16. 0 Jeg sover like godt som ellers.
1 Jeg sover ikke så godt som før.
2 Jeg våkner 1-2 timer tidligere enn ellers og har vanskelig for å sovne igjen.
3 Jeg våkner flere timer tidligere enn jeg pleide og får ikke sove igjen.

17. 0 Jeg blir ikke fortere trett enn ellers.
1 Jeg blir fortere trett enn før.
2 Nesten alt jeg gjør, blir jeg trett av.
3 Jeg er for trett til å gjøre noe som helst.

18. 0 Matlysten min er ikke dårligere enn ellers.
1 Matlysten min er ikke så god som den var før.
2 Matlysten min er mye dårligere nå.
3 Jeg har ikke matlyst i det hele tatt lenger.

19. 0 Jeg har ikke gått ned meget i vekt, om i det hele tatt noe, i den senere tid.
1 Jeg har tatt av mer enn 2 kg.
2 Jeg har tatt av mer enn 4 kg.
3 Jeg har tatt av mer enn 6 kg.

Jeg prøver bevisst å gå ned i vekt ved å spise mindre.
Ja___, Nei___

20. 0 Jeg er ikke mer bekymret for helsen min enn vanlig.
1 Jeg er bekymret over fysiske plager som verking og smerter; eller urolig mage; eller forstoppelse.
2 Jeg er meget bekymret over mine fysiske plager og det er vanskelig å tenke på stort annet.
3 Jeg er så bekymret over mine fysiske plager at jeg ikke klarer å tenke på noe annet.

21. 0 Jeg har ikke merket noen forandring i mine seksuelle interesser i det siste.
1 Jeg er mindre interessert i sex enn jeg var før.
2 Jeg er mye mindre interessert i sex nå.
3 Jeg har helt mistet interessen for sex.